SEMINAR SERIES

NUTRITIONAL DERMATOLOGY: ADVANCES FOR ACNE, ACNE INVERSA, ECZEMA, AND PSORIASIS

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Nutritional Dermatology:
Advances for Acne, Atopic Dermatitis, and Psoriasis

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Speaker Disclosure

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#BenBrownND

I am a consultant for Pure Encapsulations. I have no other relevant conflicts of interest to disclose.

2

Learning Objectives

Related to the clinical management of skin disorders with nutritional therapy:

- Review existing clinical evidence for dietary and nutrient-based supplements
- Explore recent research on new interventions
- Identify nutritional interventions that target disease subgroups
- Consider pros and cons of biomarkers and tests that may guide nutritional interventions
- Summarise pragmatic, evidence-based, personalised management

Note: supplementary notes cover topics in considerable detail. Some interventions, such as natural topical therapies, those exclusively used to prevent drug side-effects, or with limited clinical data, may not be covered due to time constraints but are in the notes for your reference.

3

Introduction

4

Unmet need

"The role of diet and nutrition in the management of chronic inflammatory skin conditions such as eczema, psoriasis and acne is one of the commonest questions asked by patients. Despite this, there is little guidance or training to help healthcare professionals provide disease-specific evidence-based recommendations to patients.."

British Journal of Dermatology, Volume 188, Issue Supplement_4, June 2023

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Education and collaboration

"We received 95 responses from dermatology nurses and 64 from doctors. Over 60% of respondents held senior positions with over 10 years of experience. Almost 100% of respondents reported being asked about diet by patients and 73.1% did not feel confident when answering these questions."

"Over 90% of respondents felt that additional nutrition training and access to specialist dietician support would be of benefit to dermatology practice."

British Journal of Dermatology, Volume 188, Issue Supplement_4, June 2023

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Acne vulgaris

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Acne vulgaris

"Acne is a chronic inflammatory disease of the pilosebaceous unit resulting from androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes*."

Lancet. 2012 Jan 28;379(9813):361-72.


Seminar

Acne vulgaris

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Gut-brain-skin axis

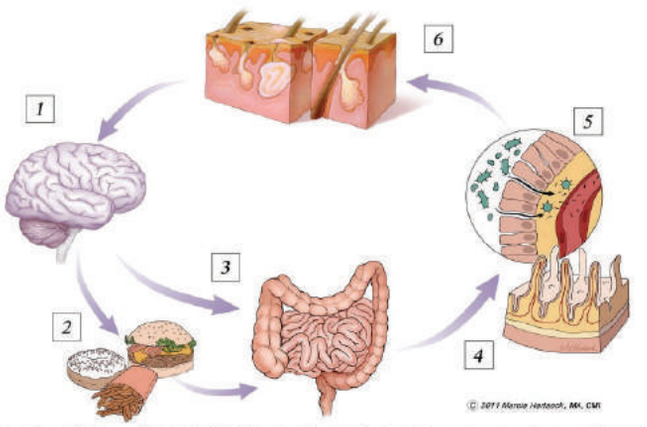

Figure 1 Potential Pathways of the Gut-Brain-Skin Axis in Acne Vulgaris: [1] Psychological distress alone or in combination with [2] high fat diet, processed comfort foods devoid of fiber, cause alterations to [3] gut motility and microbiota profile [4]. Loss of normal microbial biofilm (*Bifidobacterium* in particular) causes intestinal permeability and endotoxins gain systemic access [5]. Burden of inflammation and oxidative stress is increased, substance P is elevated, insulin sensitivity is decreased due to endotoxemia [6]. In those genetically susceptible to acne vulgaris, this cascade increases the likelihood of excess sebum production, exacerbations in acne and additional psychological distress. Both probiotics and antimicrobials may play a role in cutting off this cycle at the gut level.

Bowe W, et al. Benef Microbes. 2014 Jun 1;5(2):185-99.

9

Isotretinoin

"Individuals differ in terms of the prevalence and risk factors for isotretinoin side effects. Age, gender, dose, duration of treatment, drug interactions, comorbidities, and genetic susceptibility are a few examples of variables that may affect the frequency and intensity of adverse reactions."

Cureus. 2024 Mar 11;16(3):e55946.


Cureus

Side Effects of Treating Acne Vulgaris With Isotretinoin: A Systematic Review

Abstract

Introduction And Background

Review

Methodology

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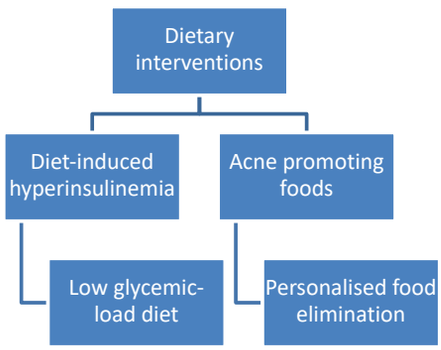
Acne vulgaris: dietary management options



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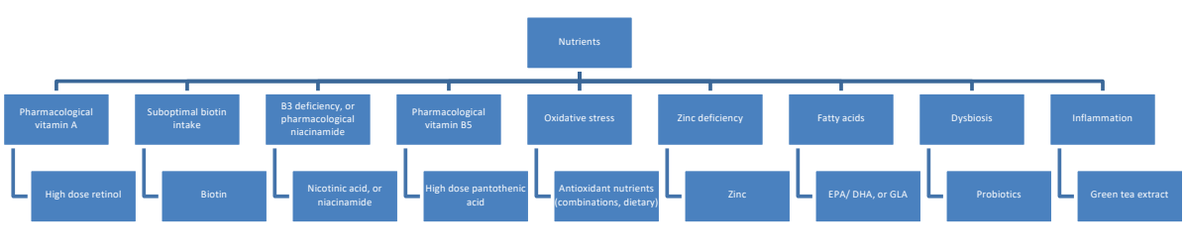
Acne vulgaris: nutrient management options



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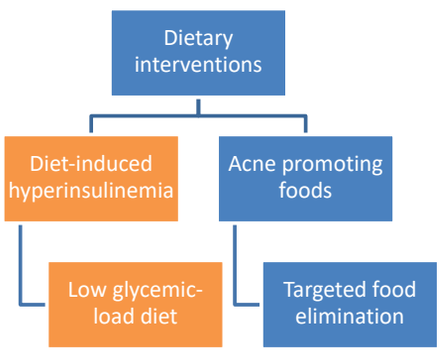
Acne vulgaris: dietary management options



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A disease of our time

In westernized societies, acne vulgaris is a nearly universal skin disease afflicting 79% to 95% of the adolescent population. Of 1200 Kitavan subjects examined (including 300 aged 15-25 years), no case of acne (grade 1 with multiple comedones or grades 2-4) was observed. Of 115 Aché subjects examined (including 15 aged 15-25 years) over 843 days, no case of active acne (grades 1-4) was observed.

Arch Dermatol. 2002 Dec;138(12):1584-90.

OBSERVATION

Acne Vulgaris

A Disease of Western Civilization

Loren Cordain, PhD; Staffan Lindeberg, MD, PhD; Magdalena Hurtado, PhD; Kim Hill, PhD; S. Boyd Eaton, MD; Jennie Brand-Miller, PhD

Background: In westernized societies, acne vulgaris is a nearly universal skin disease afflicting 79% to 95% of the adolescent population. Women and women older than 25 years, 40% to 54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men. Epidemiological evidence suggests that acne incidence rates are considerably lower in nonwesternized societies. Herein we report the prevalence of acne in 2 nonwesternized populations: the Kitavan Islanders of Papua New Guinea and the Aché hunter-gatherers of Paraguay. Additionally, we analyze how elements in nonwesternized environments may influence the development of acne.

Observations: Of 1200 Kitavan subjects examined (including 300 aged 15-25 years), no case of acne (grade 1 with multiple comedones or grades 2-4) was observed. Of 115 Aché subjects examined (including 15 aged 15-25 years) over 843 days, no case of active acne (grades 1-4) was observed.

Conclusions: The astonishing difference in acne incidence rates between nonwesternized and fully modernized societies cannot be solely attributed to genetic differences among populations but likely results from differing environmental factors. Identification of these factors may be useful in the treatment of acne in Western populations.

Arch Dermatol. 2002;138:1584-1590

ACNE AFFECTS between 40 million and 50 million individuals in the United States.[1] Although acne mainly affects adolescents, it is also present in children and adults. One study found some degree of facial acne in 54% of women and 40% of men older than 25 years.[2] In this same group, clinical facial acne affected 12% of the women and 3% of the men and persisted into middle age. Cunliffe and Gould[3] the incidence of acne is lower than in westernized populations. Schaefer,[4] a general practitioner who spent almost 30 years treating Inuit (Eskimo) people as they made the transition to modern life, reported that acne was absent in the Inuit population when they were living and eating in their traditional manner, but upon acculturation, acne prevalence became similar to that in Western societies.

For editorial comment

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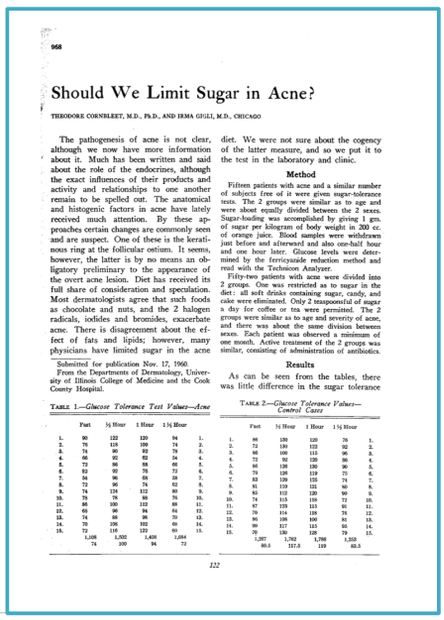
Sugar and acne

Patients with acne restricted sugar intake by eliminating soft drinks, candy, and cake, and limiting sugar in coffee or tea to 2 teaspoons per day. After a follow-up period of at least 1 month, substantial improvement or complete clearing of lesions was seen in 84% of those consuming the low-sugar diet.

Arch Dermatol 1961;83:968–969.



968

Should We Limit Sugar in Acne?

THEODORE CORNBLEET, M.D., Ph.D., AND IRMA GIGLI, M.D., CHICAGO

The pathogenesis of acne is not clear, although we now have more information about it. Much has been written and said about the role of the endocrines, although the exact influences of their products and activity and relationships to one another remains to be spelled out. The anatomical and histogenic factors in acne have lately received much attention. By these approaches certain changes are commonly seen and are suspect. One of these is the keratinous ring at the follicular ostium. It seems, however, the latter is by no means an obligatory preliminary to the appearance of the overt acne lesion. Diet has received its full share of consideration and speculation. Most dermatologists agree that such foods as chocolate and nuts, and the 2 halogen radicals, iodides and bromides, exacerbate acne. There is disagreement about the effect of fats and lipids; however, many physicians have limited sugar in the acne diet. We were not sure about the cogency of the latter measure, and so we put it to the test in the laboratory and clinic.

Method

Fifteen patients with acne and a similar number of subjects free of it were given sugar-tolerance tests. The 2 groups were similar as to age and were about equally divided between the 2 sexes. Sugar-loading was accomplished by giving 1 gm. of sugar per kilogram of body weight in 200 cc. of orange juice. Blood samples were withdrawn just before and afterward and also one-half hour and one hour later. Glucose levels were determined by the ferricyanide reduction method and read with the Technicon Analyzer.

Fifty-two patients with acne were divided into 2 groups. One was restricted as to sugar in the diet: all soft drinks containing sugar, candy, and cake were eliminated. Only 2 teaspoonsful of sugar a day for coffee or tea were permitted. The 2 groups were similar as to age and severity of acne, and there was about the same division between sexes. Each patient was observed a minimum of one month. Active treatment of the 2 groups was similar, consisting of administration of antibiotics.

Results

As can be seen from the tables, there was little difference in the sugar tolerance

Submitted for publication Nov. 17, 1960.
From the Departments of Dermatology, University of Illinois College of Medicine and the Cook County Hospital.

TABLE 1.—*Glucose Tolerance Test Values—Acne*

	Fast	½ Hour	1 Hour	1½ Hour	
1.	90	122	120	94	1.
2.	75	115	109	74	2.
3.	74	90	82	78	3.
4.	66	92	62	56	4.
5.	72	96	98	60	5.
6.	82	90	78	72	6.
7.	56	90	66	58	7.
8.	72	90	74	62	8.
9.	74	126	122	80	9.
10.	76	78	88	76	10.
11.	86	100	110	88	11.
12.	66	96	94	64	12.
13.	74	98	98	80	13.
14.	70	106	102	80	14.
15.	72	116	120	90	15.
	1,108	1,502	1,468	1,064	
	74	100	94	72	

TABLE 2.—*Glucose Tolerance Values—Control Cases*

	Fast	½ Hour	1 Hour	1½ Hour	
1.	90	130	120	78	1.
2.	72	130	120	92	2.
3.	90	100	110	96	3.
4.	72	92	120	86	4.
5.	90	130	130	90	5.
6.	70	126	119	71	6.
7.	80	130	135	74	7.
8.	81	110	131	90	8.
9.	92	112	120	90	9.
10.	74	115	116	72	10.
11.	87	135	115	95	11.
12.	70	114	130	78	12.
13.	86	108	100	81	13.
14.	90	117	115	90	14.
15.	70	130	128	79	15.
	1,207	1,782	1,790	1,253	
	80.5	117.5	119	83.5	

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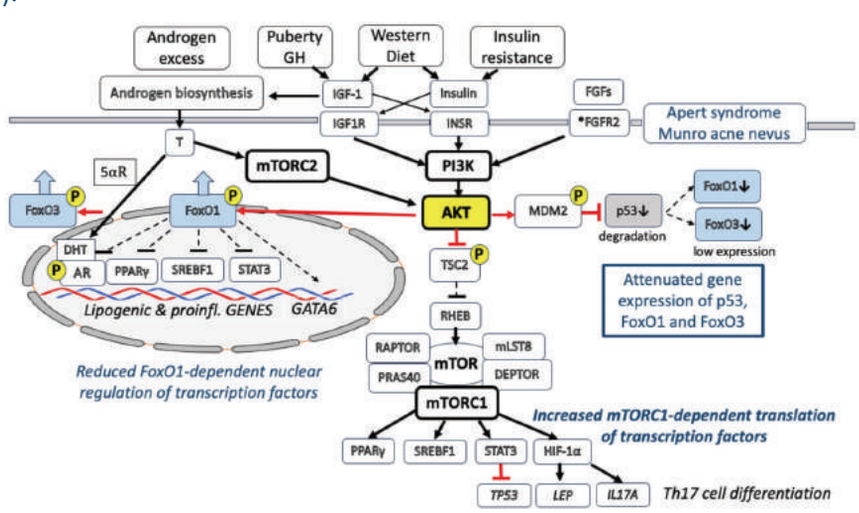
Increased IGF-1/insulin signalling due to a Western diet (hyperglycaemic carbohydrates; milk and dairy products).



Cells. 2023 Nov 10;12(22):2600.

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Dietary intervention

A 12-week intervention with a low glycemic-load (GL) diet in males aged 15 to 25 years, with mild moderate acne found that the diet reduced acne lesions, as well as weight, free androgen index, and increased IGF-1 binding protein and the ratio of saturated to monounsaturated fatty acids of skin surface triglycerides.

Am J Clin Nutr. 2007 Jul;86(1):107-15.

A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial[1–3]

Robyn N Smith, Neil J Mann, Anna Braue, Hanna Mäkeläinen, and George A Varigos

ABSTRACT

Background: Although the pathogenesis of acne is currently unknown, recent epidemiologic studies of non-Westernized populations suggest that dietary factors, including the glycemic load, may be involved.

Objective: The objective was to determine whether a low–glycemic-load diet improves acne lesion counts in young males.

Design: Forty-three male acne patients aged 15–25 y were entered into a 12-wk, parallel design, dietary intervention incorporating investigator-blinded dermatologic assessments. The experimental treatment was a low–glycemic-load diet composed of 25% energy from protein and 45% from low–glycemic-index carbohydrates. In contrast, the control diet contained conventional carbohydrate-dense foods without reference to the glycemic index. Acne lesion counts and severity were assessed during monthly visits, and insulin sensitivity (using the homeostasis model assessment) was measured at baseline and 12 wk.

Results: At 12 wk, mean (±SEM) total lesion counts had decreased more ($P = 0.03$) in the low–glycemic-load group (−25.5 ± 3.0 lesions) than in the control group (−12.6 ± 2.5). The experimental diet also resulted in a greater reduction in weight (−5.9 ± 0.8 compared with −0.5 ± 0.3 kg; $P < 0.001$) and body mass index (in kg/m^2) (−0.92 ± 0.28 compared with 0.01 ± 0.11; $P = 0.001$) and a greater improvement in insulin sensitivity (−8.22 ± 0.12 compared with 0.47 ± 0.31; $P = 0.020$) than did the control diet.

Conclusion: The improvement in acne and insulin sensitivity after a low–glycemic-load diet suggests that nutrition-related lifestyle factors may play a role in the pathogenesis of acne. However, further studies are needed to isolate the independent effects of weight loss and dietary intervention and to further elucidate the underlying pathophysiologic mechanisms. Am J Clin Nutr 2007;86:107–15.

KEY WORDS: Acne, glycemic index, glycemic load, insulin resistance, hyperinsulinemia

INTRODUCTION

Acne is a common and complex skin disease that affects individuals of all ages. In Western populations, acne is estimated to affect 79–95% of the adolescent population, 40–54% of individuals older than 25 y, and 12% of women and 3% of men by middle age (1). In contrast, acne remains rare in non-Westernized societies such as the Inuit (2), Okinawan Islanders (3), Ache hunter-gatherers, and Kitavan Islanders (4). Although familial and ethnic factors are implicated in acne prevalence, this observation is complicated by the finding that incidence rates of acne have increased with the adoption of Western lifestyles (2). These observations suggest that lifestyle factors, including diet, may be involved in acne pathogenesis.

Historically, much dietary has surrounded the subject of diet in the management of acne. In the 1930s, acne was considered to be a disease of disturbed carbohydrate metabolism because early work suggested that impaired glucose tolerance occurred in acne patients (4). On the basis of these observations and the anecdotal impressions of physicians, patients were often discouraged from eating excessive amounts of carbohydrates and high-sugar foods (5, 6). The diet and acne connection finally fell from favor in 1969 when a clinical study found no exacerbation of acne lesions in a group that ingested a chocolate bar compared with a group that ingested a placebo bar (7). Although it is the most widely cited reference disassociating diet and acne, this study has been criticized for a number of design flaws, including the similar nutritional composition of the placebo and the chocolate bar (8–10).

Recently, there has been a reappraisal of the diet and acne connection because of a greater understanding of how diet may affect endocrine factors involved in acne (1, 11). Of interest is the concept of the glycemic index (GI)—a system of classifying the glycemic response of carbohydrates. Because the GI can only be used to compare foods of equal carbohydrate contents, the glycemic load was later developed to characterize the glycemic effect of whole meals or diets (GI × available dietary carbohydrate). Cordain et al (1) postulated that high–glycemic-load diets may be a significant contributor to the high prevalence of acne seen in Western countries. The authors speculate that the frequent consumption of high-GI carbohydrates may repeatedly expose adolescents to acute hyperinsulinemia. Hyperinsulinemia has been implicated in acne pathophysiology because of its association with increased androgen bioavailability and free concentrations of insulin-like growth factor I (IGF-I) (11, 11). Therefore, we

[1] From the School of Applied Sciences, RMIT University, Melbourne, Australia (RNS and NJM); the Australian Dermatology Network, Center for Metabolic Fitness (NJM), the Department of Dermatology, Royal Melbourne Hospital, Parkville, Australia (AB and GAV); the Department of Biochemistry and Food Chemistry, Tykö University, Turku, Finland (HM); and the Department of Dermatology, Royal Children's Hospital, Parkville, Australia (GAV).

[2] Supported by a research grant from Meat and Livestock Australia.

[3] Address reprint requests to RN Smith, School of Applied Sciences, RMIT University, GPO Box 2476V, Melbourne, Victoria, Australia, 3001. E-mail: robyn.smith@rmit.edu.au.

Received September 21, 2006.

Accepted for publication February 9, 2007.

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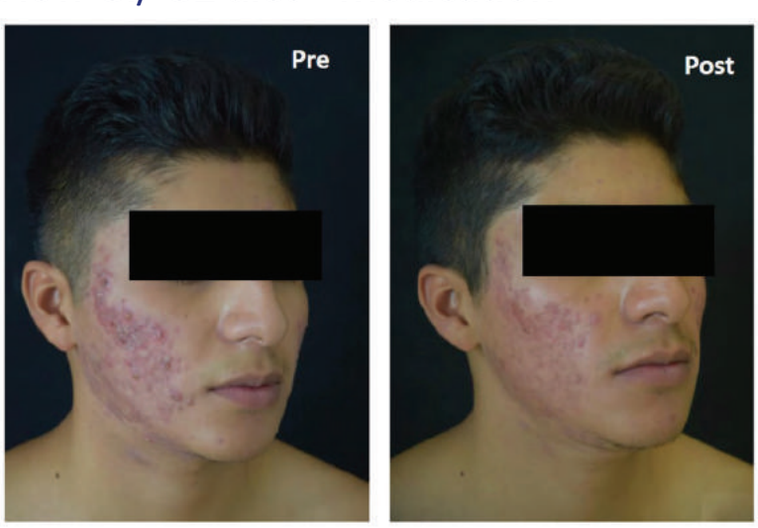
Effects of a low GI/ GL diet + medication



Int J Dermatol. 2023 Jan;62(1):e39-e42.

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Low glycemic load diet

Intervention	Discussion	Guidance
Low glycemic load diet	High-GL diets and resultant insulin resistance and hyperinsulinemia contribute to acne development, while low-GL diets may reduce acne severity.	Limit intake of high-GL foods including refined grains and sugars as well as total available sugars from carbohydrate-rich foods.

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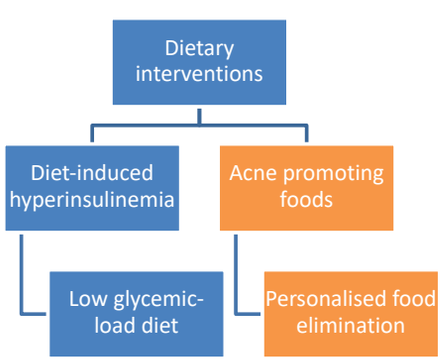
Acne vulgaris: dietary management options



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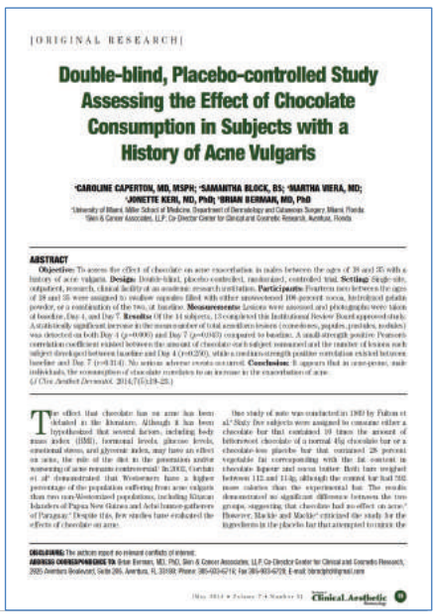
Cocoa

A single-dose of pure cocoa resulted in a significant dose-response related increase in acne lesions in patients with pre-existing acne within 4-days.

J Clin Aesthet Dermatol. 2014 May;7(5):19-23.



[ORIGINAL RESEARCH]

Double-blind, Placebo-controlled Study Assessing the Effect of Chocolate Consumption in Subjects with a History of Acne Vulgaris

*CAROLINE CAPERTON, MD, MSPH; *SAMANTHA BLOCK, BS; *MARTHA VIERA, MD; *JONETTE KERI, MD, PhD; †BRIAN BERMAN, MD, PhD

ABSTRACT

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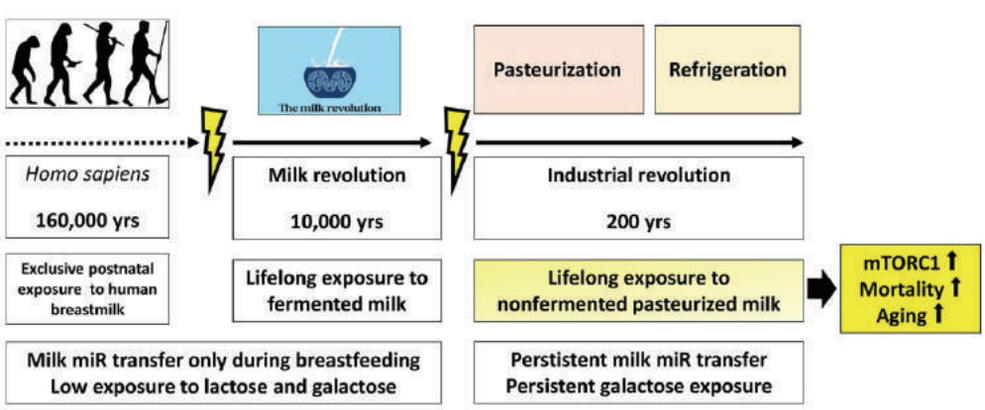
Pasteurized non-fermented cow's milk, but not fermented milk, is a promoter of mTORC1.



Ageing Res Rev. 2021 May;67:101270.

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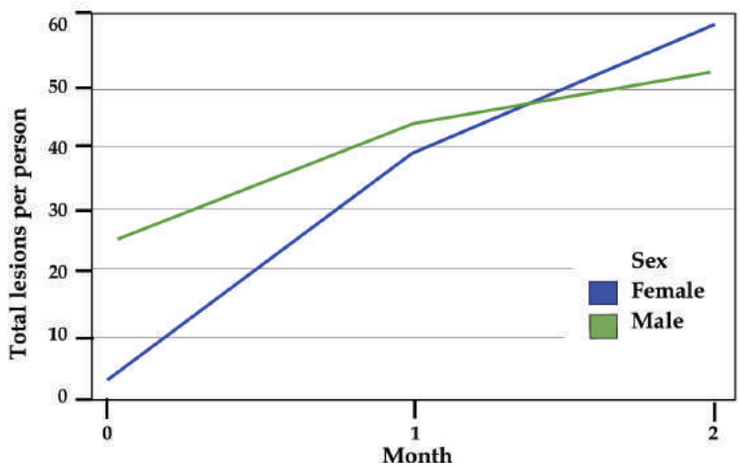
Protein supplements and acne lesions

Total number of acne lesions per person by sex in the months after beginning protein supplement use in a young adult population.



Pontes Tde C, et al. An Bras Dermatol. 2013 Nov-Dec;88(6):907-12.

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Acne promoting foods

Intervention	Discussion	Guidance
Acne promoting foods	Cow's milk, whey protein, and cocoa have been linked to the development and/or exacerbation of acne. So have dietary supplements vitamin B12 and Kelp.	Consider limiting or eliminating exposure dietary cow's milk, whey protein and cocoa if suspected to be contributing to symptoms. High dose vitamin B12 and Kelp supplements may also contribute to acne-like symptoms.

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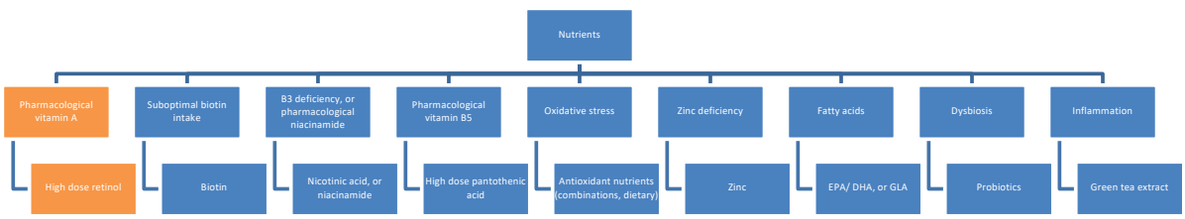
Acne vulgaris: nutrient management options



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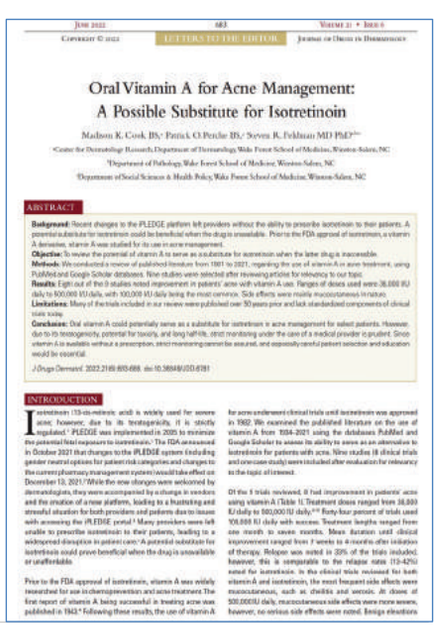
Vitamin A

A review of clinical trials of vitamin A for the treatment of acne identified eight prospective studies published between 1943 and 1981. Of these all the studies reported improvement apart from one study that may have been impacted by an insufficient treatment duration. The treatment response was 82%, which is similar to the clearance rate of 85% observed with isotretinoin.

J Drugs Dermatol. 2022 Jun 1;21(6):683-686.



LETTERS TO THE EDITOR

Oral Vitamin A for Acne Management: A Possible Substitute for Isotretinoin

ABSTRACT

INTRODUCTION

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Vitamin A

Intervention	Discussion	Guidance
Vitamin A	Vitamin A may be a suitable alternative to isotretinoin (a vitamin A analogue).	Consider a course of >100,000 IU/ daily for 4-months. Although relatively safe, monitor for hypervitaminosis A and avoid in pregnancy.

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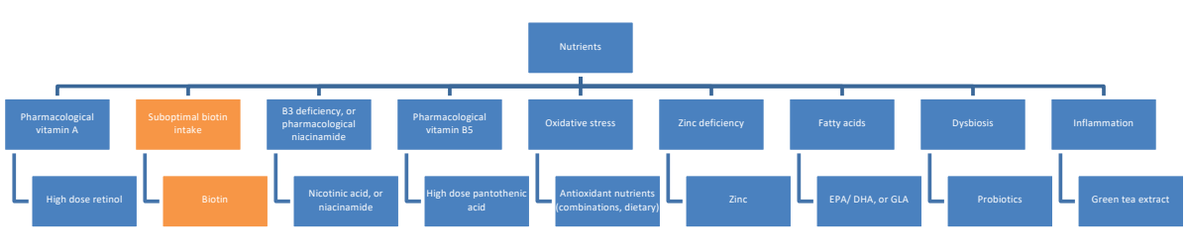
Acne vulgaris: nutrient management options



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Biotin

In a clinical trial (n=60), biotin supplementation (10 mg/ day) was added to isotretinoin therapy over 4-months. Compared to isotretinoin alone, biotin decreased sign of hair thinning and loss (telogen and increased anagen hair rates) and maintained skin hydration.

Int J Dermatol. 2021 Aug;60(8):980-985.

International Journal of Dermatology

Report

Evaluation of biophysical skin parameters and hair changes in patients with acne vulgaris treated with isotretinoin, and the effect of biotin use on these parameters

Sema E. Aksac[1], MD, Serap G. Bilgili[2], MD, Goknur O. Yavuz[2], MD, Ibrahim H. Yavuz[2], MD, Murat Aksac[3], ND and Ayse S. Karadag[4], MD

pure encapsulations

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Biotin

Intervention	Discussion	Guidance
Biotin	Biotin deficiency may be associated with acne, but more evidence is needed.	Consider >30 µg daily if risk factors for deficiency are present. Reduces mucocutaneus side-effects isotretinoin of at 10 mg daily.

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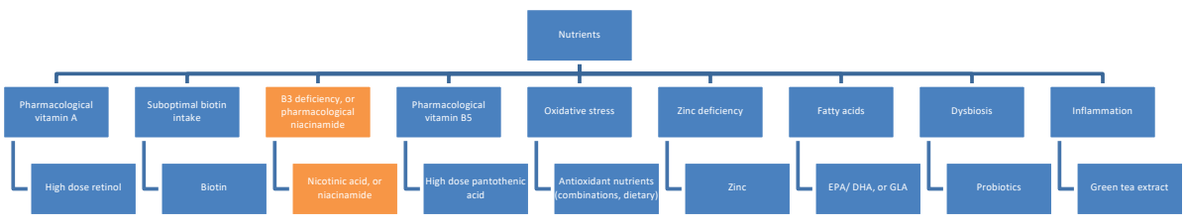
Acne vulgaris: nutrient management options



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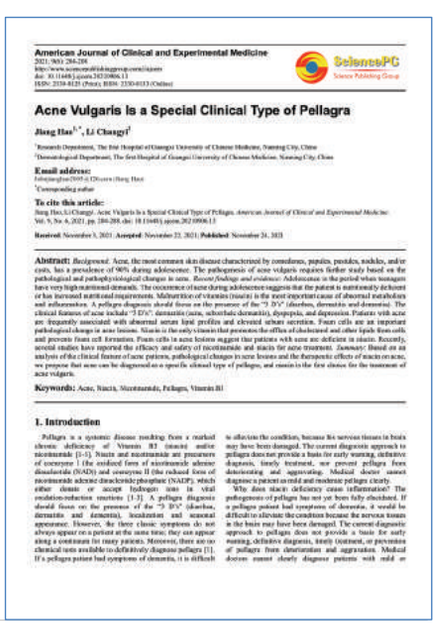
Vitamin B3

”A pellagra diagnosis should focus on the presence of the “3 D’s” (diarrhoea, dermatitis and dementia). The clinical features of acne include “3 D’s”: dermatitis (acne, seborrheic dermatitis), dyspepsia, and depression.”

American Journal of Clinical and Experimental Medicine. Vol. 9, No. 6, 2021, pp. 204-208.



American Journal of Clinical and Experimental Medicine

Acne Vulgaris Is a Special Clinical Type of Pellagra

Jiang Hao[1,*], Li Changyi[2]

[1]Research Department, The First Hospital of Changzi University of Chinese Medicine, Nanning City, China
[2]Dermatological Department, The First Hospital of Guangxi University of Chinese Medicine, Nanning City, China

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Abstract: *Background:* Acne, the most common skin disease characterized by comedones, papules, pustules, nodules, and/or cysts, has a prevalence of 90% during adolescence. The pathogenesis of acne vulgaris requires further study based on the pathological and pathophysiological changes in acne. *Recent findings and evidence:* Adolescence is the period when teenagers have very high nutritional demands. The occurrence of acne during adolescence suggests that the patient is nutritionally deficient or has increased nutritional requirements. Malnutrition of vitamins (niacin) is the most important cause of abnormal metabolism and inflammation. A pellagra diagnosis should focus on the presence of the “3 D’s” (diarrhea, dermatitis and dementia). The clinical features of acne include “3 D’s”: dermatitis (acne, seborrheic dermatitis), dyspepsia, and depression. Patients with acne are frequently associated with abnormal serum lipid profiles and elevated sebum secretion. Foam cells are an important pathological change in acne lesions. Niacin is the only vitamin that promotes the efflux of cholesterol and other lipids from cells and prevents foam cell formation. Foam cells in acne lesions suggest that patients with acne are deficient in niacin. Recently, several studies have reported the efficacy and safety of nicotinamide and niacin for acne treatment. *Summary:* Based on an analysis of the clinical feature of acne patients, pathological changes in acne lesions and the therapeutic effects of niacin on acne, we propose that acne can be diagnosed as a specific clinical type of pellagra, and niacin is the first choice for the treatment of acne vulgaris.

Keywords: Acne, Niacin, Nicotinamide, Pellagra, Vitamin B3

1. Introduction

Pellagra is a systemic disease resulting from a marked chronic deficiency of Vitamin B3 (niacin) and/or nicotinamide [1-3]. Niacin and nicotinamide are precursors of coenzyme I (the oxidized form of nicotinamide adenine dinucleotide (NAD)) and coenzyme II (the reduced form of nicotinamide adenine dinucleotide phosphate (NADP), which either donate or accept hydrogen ions in vital oxidation-reduction reactions [1-3]. A pellagra diagnosis should focus on the presence of the “3 D’s” (diarrhea, dermatitis and dementia). Inconstant and seasonal appearance. However, the three classic symptoms do not always appear on a patient at the same time; they can appear along a continuum for many patients. Moreover, there are no chemical tests available to definitively diagnose pellagra [1]. If a pellagra patient had symptoms of dementia, it is difficult to alleviate the condition, because his nervous tissues in brain may have been damaged. The current diagnostic approach to pellagra does not provide a basis for early warning, definitive diagnosis, timely treatment, nor prevent pellagra from deteriorating and aggravating. Medical doctor cannot diagnose a patient as mild and moderate pellagra clearly.

Why does niacin deficiency cause inflammation? The pathogenesis of pellagra has not yet been fully elucidated. If a pellagra patient had symptoms of dementia, it would be difficult to alleviate the condition because the nervous tissues in the brain may have been damaged. The current diagnostic approach to pellagra does not provide a basis for early warning, definitive diagnosis, timely treatment, or prevention of pellagra from deterioration and aggravation. Medical doctors cannot clearly diagnose patients with mild or

32

Nicotinamide

An 8-week clinical trial of nicotinamide (750 mg daily), zinc (25 mg), copper (1.5 mg), and folic acid (500 mcg) reported a significant improvement in acne severity with treatment.

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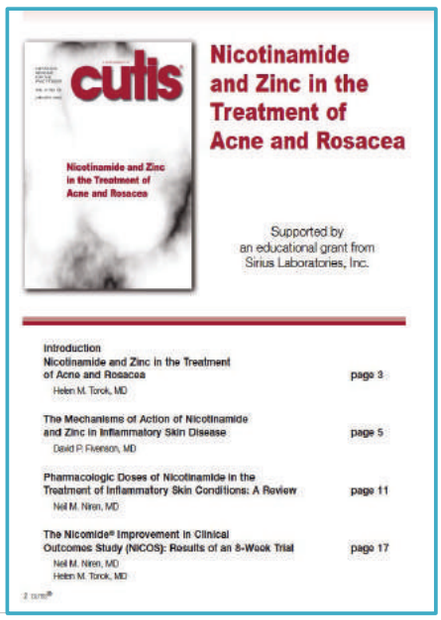
Cutis. 2006 Jan;77(1 Suppl):17-28.



33

Vitamin B3

Intervention	Discussion	Guidance
Vitamin B3	Subclinical vitamin B3 deficiency may be associated with acne. Nicotinamide has pharmacological anti-inflammatory effects.	Nicotinic acid at a dose of 500 mg three times daily could be trialed, however patients should be counseled about flushing. A minimum 8-week course of 600 mg to 750 mg of nicotinamide may help reduce acne severity.

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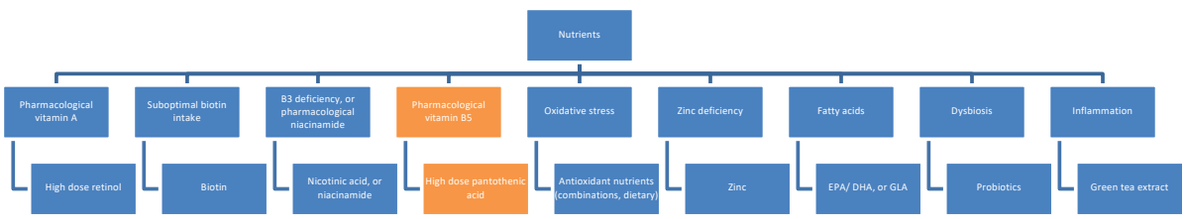
Acne vulgaris: nutrient management options



35

Pantothenic acid

A 12-week clinical study in adults with facial acne found that pantothenic acid (2.2 g daily) reduced total facial lesion count and inflammatory blemishes.

Dermatol Ther (Heidelb). 2014 Jun;4(1):93-101.

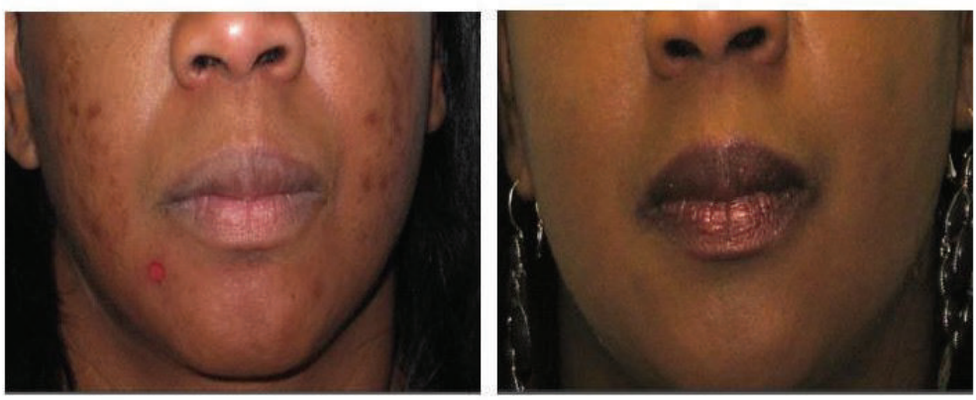
ORIGINAL RESEARCH

A Randomized, Double-Blind, Placebo-Controlled Study of a Novel Pantothenic Acid-Based Dietary Supplement in Subjects with Mild to Moderate Facial Acne

ABSTRACT

36

Pantothenic acid



Baseline Week 12

Dermatol Ther (Heidelb). 2014 Jun;4(1):93-101.

37

Vitamin B5

Intervention	Discussion	Guidance
Vitamin B5	High-dose pantothenic acid has shown some evidence of benefit.	A minimum 12-week course of at least 2.2 g of pantothenic acid could be considered.

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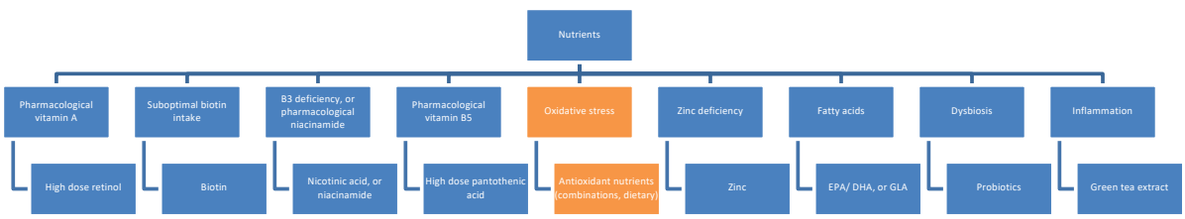
Acne vulgaris: nutrient management options



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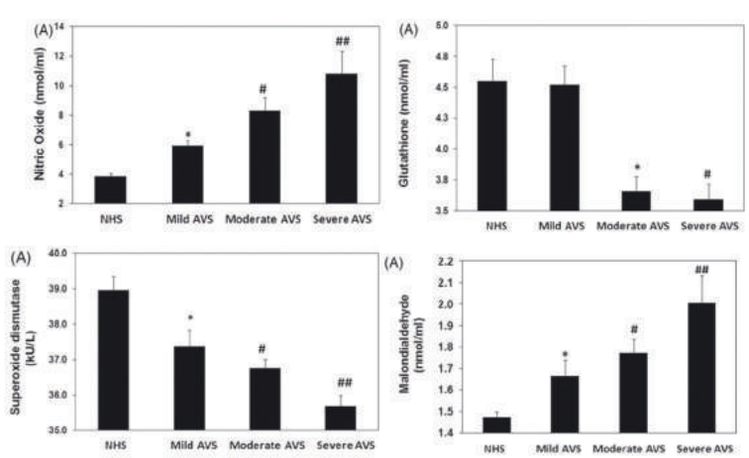
Oxidative stress: correlation with diseasease activity

Biomarkers of oxidative and nitrosative stress in serum acne vulgaris (AVS) with mild (n = 20), moderate (n = 23), and severe (n = 7) scores and in normal human sera (NHS, n = 40).



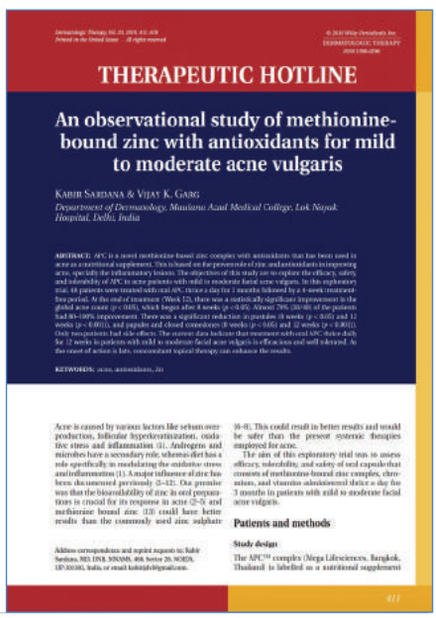
Al-Shobaili HA, et al. Biochemical markers of oxidative and nitrosative stress in acne vulgaris: correlation with disease activity. J Clin Lab Anal. 2013 Jan;27(1):45-52.

40

Antioxidants

An antioxidant complex providing zinc methionine (35 mg), ascorbic acid (180 mg), mixed carotenoids (18 mg), vitamin E as D-alpha tocopheryl acetate (45 IU) and chromium picolinate (36 mcg) daily, in divided doses, resulted in a significant reduction in clinical symptoms over 12-weeks.

Dermatol Ther. 2010 Jul-Aug;23(4):411-8.



THERAPEUTIC HOTLINE

An observational study of methionine-bound zinc with antioxidants for mild to moderate acne vulgaris

KABIR SARDANA & VIJAY K. GARG

Department of Dermatology, Maulana Azad Medical College, Lok Nayak Hospital, Delhi, India

Patients and methods

Study design

41

Antioxidant nutrients

Intervention	Discussion	Guidance
Antioxidant nutrients	Redox imbalance and inflammation are intrinsic to acne pathophysiology, can be modulated by antioxidant nutrients and improve the disease course.	Consider multi-nutrient formulations designed to modulates oxidative stress. Improve dietary antioxidant intake with foods rich in antioxidant vitamins (especially vitamins C and E), carotenoids and polyphenols.

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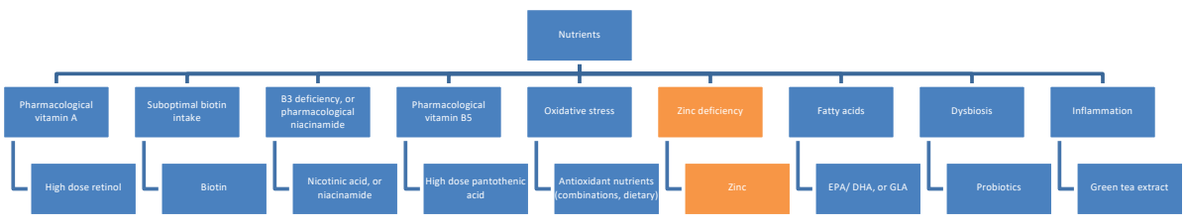
Acne vulgaris: nutrient management options



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Zinc

"Minocycline nevertheless showed a 9% superiority in action at 1 month and one of 17% at 3 months, with respect to the mean change in lesion count. Regarding safety, the majority of the adverse effects of zinc gluconate and of minocycline concerned the gastrointestinal system and were moderate (5 dropouts with zinc gluconate and 4 with minocycline)."

Dermatology. 2001;203(2):135-40.

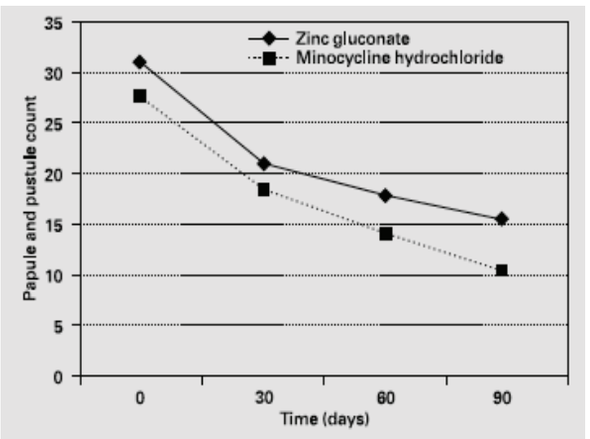
Pharmacology and Treatment

Multicenter Randomized Comparative Double-Blind Controlled Clinical Trial of the Safety and Efficacy of Zinc Gluconate versus Minocycline Hydrochloride in the Treatment of Inflammatory Acne vulgaris

Brigitte Dreno[a] Dominique Moyse[b] Mohsen Alirezai[c] Pierre Arribiand[d] Nicole Auffret[e] Claire Beylot[f] Isaac Bodokh[g] Martine Chivot[h] François Daniel[i] Philippe Humbert[j] Joan Moynadier[k] Florence Poli[l] and private-practice dermatologists coordinated by the Acne Research and Study Group

KARGER

Zinc



Dermatology. 2001;203(2):135-40.

45

Zinc

Intervention	Discussion	Guidance
Zinc	Zinc deficiency is common in acne, but zinc may also have direct disease-modifying effects.	Supplementation with 30 mg elemental zinc daily would be useful in deficiency but may also be useful as a treatment in inflammatory acne independent of overt deficiency.

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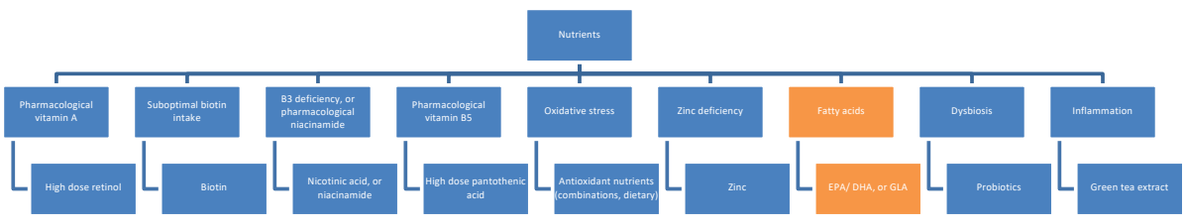
Acne vulgaris: nutrient management options



47

Fatty acids

A 10-week, randomized controlled trial in adults with mild to moderate acne found that supplementation with EPA and DHA (2000 mg) or gamma-linoleic acid (400mg from borage oil) found that both treatment reduced acne severity and inflammation.

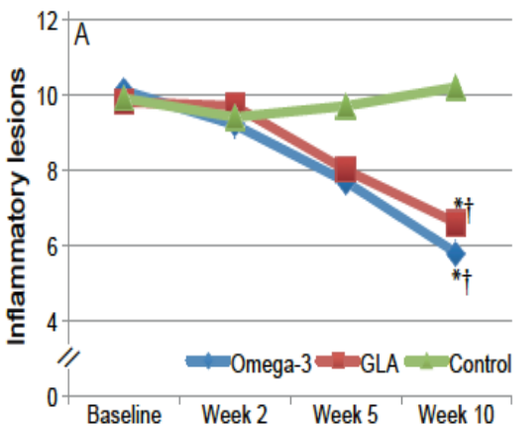
Acta Derm Venereol. 2014 Sep;94(5):521-5.

INVESTIGATIVE REPORT

Effect of Dietary Supplementation with Omega-3 Fatty Acid and Gamma-linolenic Acid on Acne Vulgaris: A Randomised, Double-blind, Controlled Trial

48

Fatty acids



Acta Derm Venereol. 2014 Sep;94(5):521-5.

49

Fatty acids

Intervention	Discussion	Guidance
Fatty acids	Clinical interventions have found a good clinical response to EPA and DHA and/ or GLA.	A minimum 12-week course of fish oil providing around 1000 mg EPA and DHA/ or 320 mg of GLA could be considered in patients with acne.

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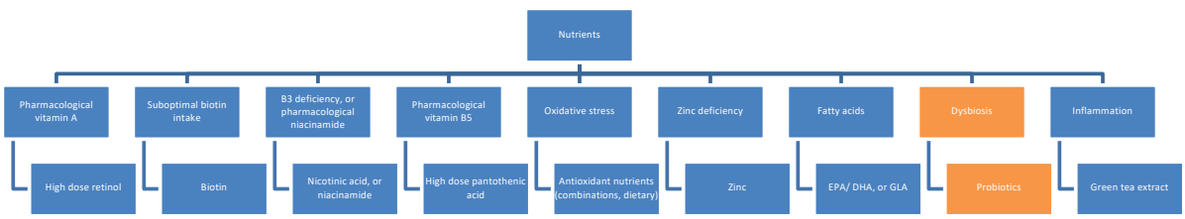
Acne vulgaris: nutrient management options



51

L rhamnosus GG

A 12-week clinical trial of a *L rhamnosus* GG (3 billion CFU daily) in adults reduced clinical symptoms of acne and improved expression of genes involved in insulin signaling in their skin.

Rating	Probiotic group (n=10)	Placebo group (n=10)
Worsened	0 (0%)	0 (0%)
Unchanged	2 (20%)	9 (90%)
Improved	6 (60%)	1 (10%)
Markedly improved	2 (20%)	0 (0%)
Resolved	0 (0%)	0 (0%)

Benef Microbes. 2016 Nov 30;7(5):625-630.

Beneficial Microbes, 2016 online ARTICLE IN PRESS

Supplementation with *Lactobacillus rhamnosus* SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne

RESEARCH ARTICLE

Abstract

1. Introduction

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Probiotics

Intervention	Discussion	Guidance
Probiotics	Probiotics can modulate microbiome composition and/ or function and are emerging as a therapeutic option for improving the function of the gut-brain-skin axis.	Evidence suggests probiotics, regardless of the type of product or strains used, may improve acne symptoms. It appears prudent to trial a course of probiotics in patients with acne.

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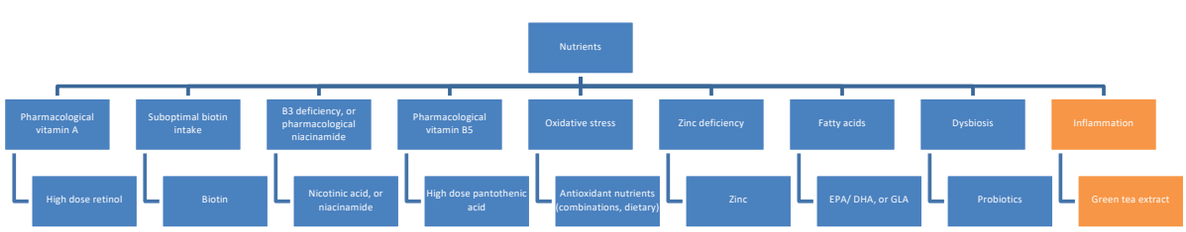
Acne vulgaris: nutrient management options



54

Green tea extract

A 4-week clinical trial in adult women with acne found that green tea extract resulted in a statistically significant improvement in total and inflammatory acne lesions.

Complement Ther Med. 2016 Apr;25:159-63.


Complementary Therapies in Medicine

Does supplementation with green tea extract improve acne in post-adolescent women? A randomized, double-blind, and placebo-controlled clinical trial

55

Green tea

Intervention	Discussion	Guidance
Green tea extract	Green tea extract is a safe and useful intervention for reducing acne severity.	A 4-week course of green tea extract providing 856mg of epigallocatechin-3-gallate daily may be useful, but care should be taken with long-term use due to hepatic side-effects.

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Atopic dermatitis

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Atopic dermatitis

"Atopic dermatitis (AD) is a common eczematous skin disorder affecting 2-20% of the general population with age and ethnic differences. AD is characterized by chronic cutaneous inflammation and dry skin with epidermal barrier dysfunction. Intense pruritus is the major and burdensome symptom of AD."

Allergol Int. 2017 Jan 2. pii: S1323-8930(16)30171-X.

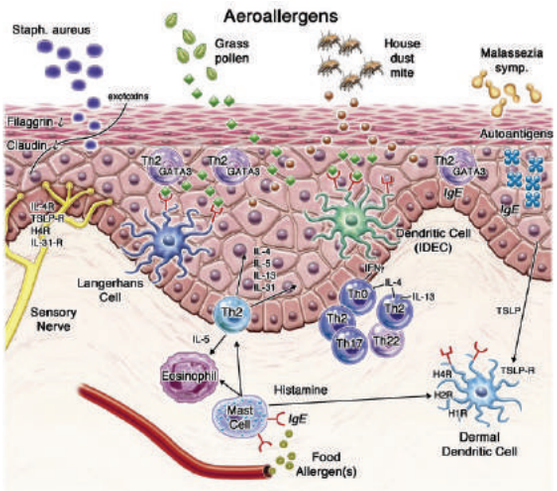
Allergology International

Review Article

Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies

58

Cellular and molecular immunologic mechanisms



J Allergy Clin Immunol. 2016 Aug;138(2):336-49.

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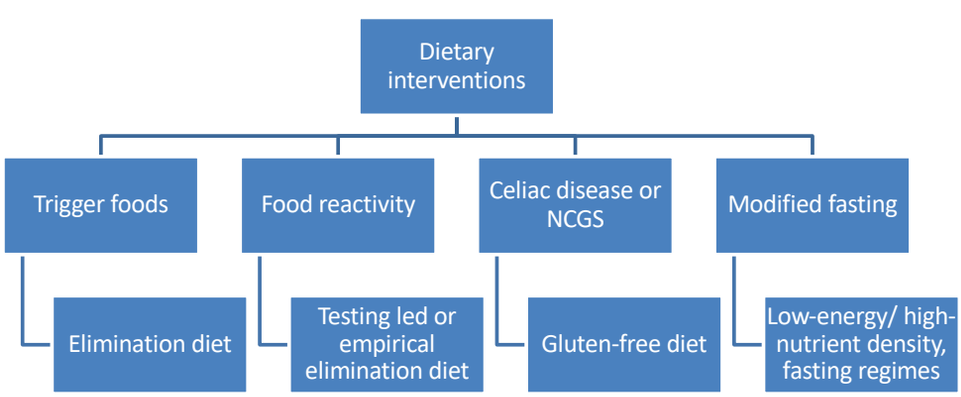
Atopic dermatitis: dietary management options



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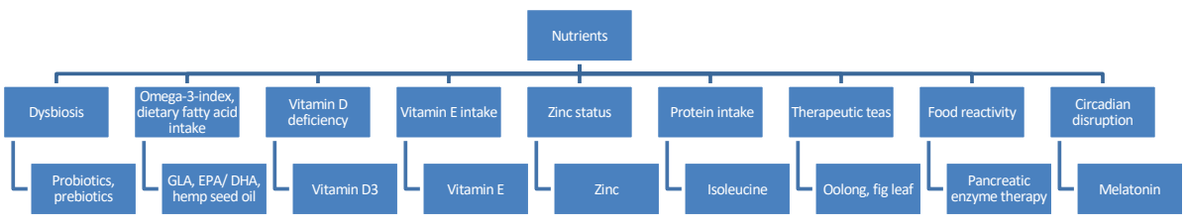
Atopic dermatitis: nutrient management options



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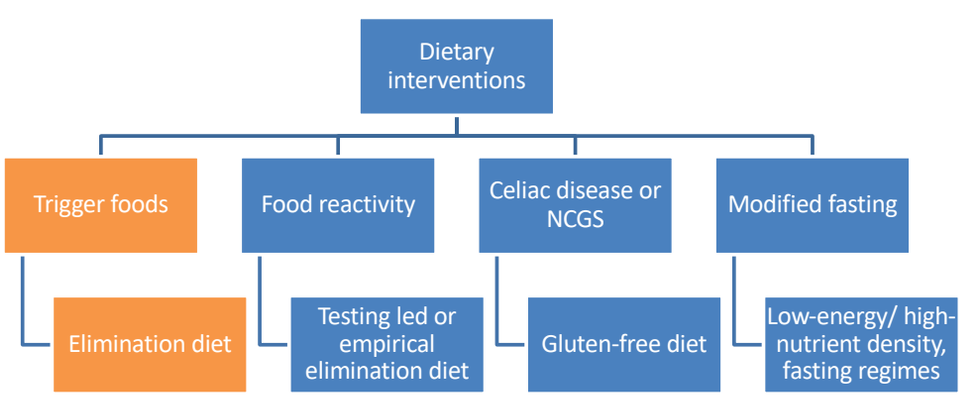
Atopic dermatitis: dietary management options



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Food triggers

In a double-blind placebo-controlled food challenge, 46% of children with atopic dermatitis experienced a food reaction to cow's milk, hen's egg, wheat or soy, with immediate-onset reactions tending to produce erythema or urticaria, and delayed-onset reactions typically producing a flare up of preexisting lesions.

Clin Exp Allergy. 2004 May;34(5):817-24.

Clin Exp Allergy 2004; 34:817–824 doi:10.1111/j.1365-2222.2004.01953.x

Late eczematous reactions to food in children with atopic dermatitis

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*Department of Dermatology and Allergology, Hannover Medical University, Germany and †Department of Pediatric Pulmonology and Neonatology, Hannover Medical University, Germany

Summary

Background Food allergy is a common problem in patients with atopic dermatitis (AD), particularly in children. While immediate reactions to food are well characterized, the importance of food as a provocation factor for late eczematous reactions has been a subject of debate for several decades.

Objective To investigate the importance of food for the induction of late eczematous reactions in children with AD and to correlate the clinical outcome to the results of specific IgE determinations and atopy patch tests (APTs).

Methods One hundred and six double-blind placebo-controlled food challenges (DBPCFCs) to cow's milk, hen's egg, wheat and soy in 64 children with AD (median age 2 years) were analysed retrospectively. Total and food-specific IgE were determined by CAP RAST FEIA and APTs with native foods/stuff were performed. The diagnostic values of specific IgE and APT results were calculated.

Results Forty-nine (46%) of the challenges were related to a clinical reaction. An exacerbation of AD (late eczematous reaction) commonly occurred 24h after the ingestion of food. Isolated late eczematous reactions were seen in 12% of all positive challenges. Forty-five percent of the positive challenges were associated with late eczematous responses, which followed immediate-type reactions. The sensitivity of food-specific IgE and the APT was 76% and 70%, respectively. Specific IgE and APT were often false positive, which resulted in low positive predictive values (64% and 45%, respectively).

Conclusions Late eczematous reactions may often be observed upon food challenge in children with AD. Due to the poor reliability of food-specific IgE and APT results DBPCFCs have still to be regarded as the gold standard for the appropriate diagnosis of food responsive eczema in children with AD.

Keywords atopic dermatitis, atopy patch test, food allergy, food challenge, food responsive eczema, food-specific IgE
Submitted 1 August 2003; revised 16 December 2003; accepted 2 February 2004

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, which commonly begins in early infancy, runs a course of exacerbations and remissions and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and subsequently sleeplessness are hallmarks of AD [1]. Numerous trigger factors have been identified for AD over the last decades, such as inhalative allergens, food allergens, irritative substances and infectious microorganisms like *Staphylococcus aureus* and *Malassezia furfur* [2–4]. There is substantial evidence that foods like cow's milk and hen's egg are major provocation factors for the flares of AD in infancy, while inhalant allergens and pollen-related foods are of greater importance in adults [5–9].

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According to Wüthrich, three patterns of cutaneous reactions to food may occur in patients with AD upon oral challenge [10]:

(i) Immediate-type reactions such as urticaria, angioedema and erythema, commonly occurring a few minutes after ingestion of food without an exacerbation of AD. Additionally, gastrointestinal, respiratory and cardiovascular symptoms may evolve.
(ii) Pruritus occurring soon after the ingestion of food with subsequent scratching leading to an exacerbation of AD.
(iii) Exacerbations of AD occurring after 6–48 h termed late reactions. Late reactions may occur also after an immediate-type response.

The prevalence of food allergy in infants with AD was reported in a range between 20% and 80% in various studies, and may be estimated at 30% [11–13]. Hen's egg, cow's milk, soy and wheat account for about 90% of allergenic foods in children with AD [11, 14]. Dependent on the kind of food,

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Trigger foods

Intervention	Discussion	Guidance
Trigger foods	Foods that trigger symptoms are relatively common but often overlooked, and avoidance may help control symptoms.	Trigger foods can be identified based on patient history; however, people may not have previously associated foods with a flare up in their symptoms. Routine elimination and re-challenge with cow's milk, egg, wheat or soy may be useful. Re-challenge in a medical setting may be advise if there is risk of anaphylaxis.

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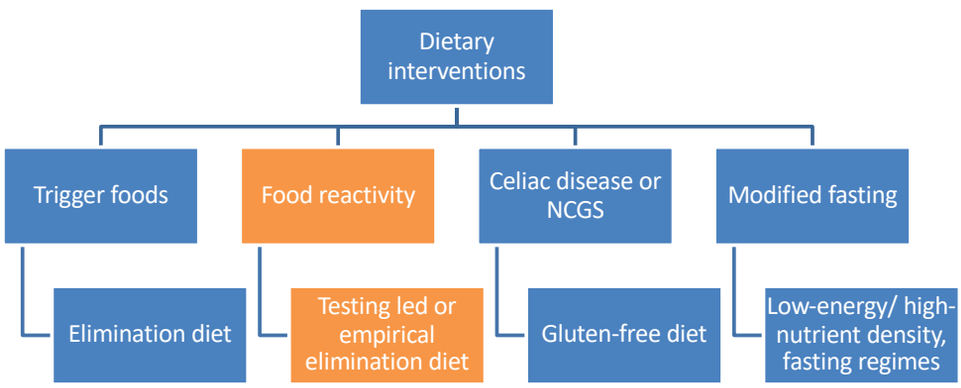
Atopic dermatitis: dietary management options



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Elimination diets

- ✓ Elimination diets are an important consideration in atopic dermatitis and can result in good clinical improvement.
- ✓ The failure of some studies to produce benefits, however, may be due to lack of personalization i.e. non-discriminate elimination of foods without assessment of sensitivity.
- ✓ Dietary removal of industrial food additives and monosodium glutamate have been shown to reduce atopic dermatitis.
- ✓ Prolonged elimination diets in young children could result in increased risk of immediate-onset and severe allergic reactions, including anaphylaxis.

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Elimination + functional foods

In children, a personalized elimination diet combined with consumption of antioxidant and omega-3 fatty acids rich-foods found that this approach significantly improved nutritional intakes, reduced disease severity, and improved the growth status, as measured by height and weight scores in children.

Asia Pac J Clin Nutr. 2016 Dec;25(4):716-728

716 Asia Pac J Clin Nutr 2016;25(4):716-728

Original Article

Children with atopic dermatitis in Daejeon, Korea: individualized nutrition intervention for disease severity and nutritional status

Seong Hee Kim MSc[1], Jae Ho Lee MD, PhD[2], Sun Yung Ly PhD[1]

[1]Department of Food and Nutrition, Chungnam National University, Republic of Korea
[2]Department of Pediatrics, College of Medicine, Chungnam National University, Republic of Korea

Background and Objectives: Atopic dermatitis is one of the most common pediatric chronic inflammatory skin diseases, and certain food allergens and nutrients are closely related to the development and severity of atopic dermatitis. While avoidance of the causative foods is considered the mainstay of treatment, unverified excessive restriction might induce unnecessary limitations in the food intake, consequently leading to nutritional deficiencies and poor growth. This study aimed to identify the characteristics and nutrient intake status in children with atopic dermatitis and to investigate the effects of individualized nutrition intervention. **Methods and Study Design:** We retrospectively reviewed electronic medical records of 77 pediatric patients with atopic dermatitis who received 4 months of individualized nutrition intervention combined with an elimination diet. The patient characteristics, nutrient intake status, and clinical status were examined before and after the intervention. **Results:** Before the intervention, 5 children had a weight for height z-score below -2.0, and 48.1% had experienced food restriction; these children showed a significantly higher SCORing of Atopic Dermatitis index than those without experiences, with the number of restricted foods before the intervention positively correlating with the disease severity. The intakes of n-6 and n-3 fatty acids, calcium, folate, and vitamin D were lower than the recommended nutrient intakes for Koreans. After the intervention, the weight for height z-score of 35 children was significantly increased and their SCORing of Atopic Dermatitis index was significantly reduced ($p<0.05$). **Conclusions:** Individualized nutrition intervention appears useful for alleviating the severity of atopic dermatitis and improving the growth status by improving the nutrient intake.

Key Words: atopic dermatitis, individualized nutrition intervention, SCORAD index, growth, nutritional status

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, and frequently begins already in early infancy.[1] Although it varies between different regions, the prevalence of childhood eczema or AD is continuously increasing worldwide. The 2003 National Survey of Children's Health in the US showed that the lifetime prevalence of AD was 10.7% in children under 18 years,[2] while the International Study of Asthma and Allergies in Childhood reported one-year prevalence rates of up to 20% in Australasia, England, and Scandinavia.[3] Further, the Korea National Health and Nutrition Examination Survey data showed an AD rate of 13.0% in children aged 1 to 18 years.[4]

Numerous trigger factors of AD have been verified in recent decades, including genetic factors,[5] inhaled allergens, food allergens and certain nutrients,[6] irritating substances, and infectious microorganisms.[7] Of these factors, the major food allergens, including egg white, cow's milk, soybeans, wheat, and peanuts, have been reported to be more strongly related to AD in childhood than in adults.[8,9] The clinical spectrum of food allergy (FA) ranges from mild skin irritation to severe life-threatening anaphylaxis,[10] and AD secondary to FA includes skin disorders such as incessant pruritus, xerosis, eczematous lesions, and lichenification.

These various skin symptoms of AD secondary to FA are caused by adverse cellular responses activated through specific antibodies against the food allergen,[11] mediated by both immunoglobulin E (IgE) and non-IgE mechanisms. It has been demonstrated that IgE-mediated FA appears as acute reactions such as localized urticaria and anaphylaxis, whereas non IgE-mediated FA usually results in delayed respiratory, gastrointestinal, and cutaneous symptoms.[12] Moreover, while it has been well established that IgE-mediated FA plays a central role in the immunopathogenesis of AD,[13] non-IgE-mediated responses have also been recently reported as a major characteristic of AD. Direct exacerbation of AD with devel-

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Email: sunly@cnu.ac.kr

Manuscript received 01 April 2015. Initial review completed 24 June 2015. Revision accepted 14 July 2015.
doi: 10.6133/apjcn.092015.31

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Personalised elimination diet

Intervention	Discussion	Guidance
Personalized elimination diet	Elimination diets can help reduce symptoms by limiting exposure to allergenic foods that are exacerbating atopy.	An elimination diet can be based on food sensitivity testing, including IgG. Without testing, an elimination and re-challenge with major and/ or suspected food allergens may still be useful. Reducing exposure to food additives and MSG may be useful.
Functional foods	Advice to increase intake of foods with anti-allergic, anti-inflammatory effects such as antioxidant and omega-3 fatty acids rich-foods has been shown to complement an elimination diet.	Advise patient to increase intake of polyphenol-rich fruits and vegetable foods and beverages, additionally increase intake of omega-3 rich foods such as nuts, seeds, and fish.

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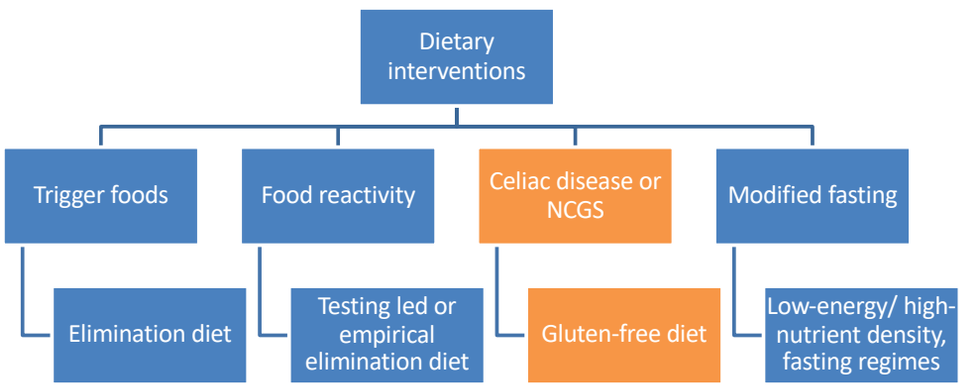
Atopic dermatitis: dietary management options

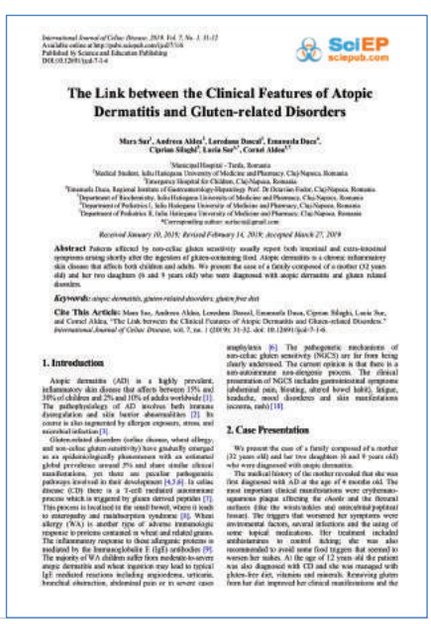


69

Gluten free diet

A case report described marked symptomatic improvement in a mother and her two daughters, all diagnosed with atopic dermatitis, after gluten removal. Importantly, while the mother was diagnosed with celiac disease her daughters both tested negative for celiac disease.

International Journal of Celiac Disease, *7*(1), 31-32.



The Link between the Clinical Features of Atopic Dermatitis and Gluten-related Disorders

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Gluten free diet

Intervention	Discussion	Guidance
Gluten free diet	Celiac disease and NCGS may be associated with atopic dermatitis, and a gluten-free diet may be supportive.	Screen for celiac disease due to higher prevalence in atopic dermatitis. Consider NCGS and a gluten-free diet.

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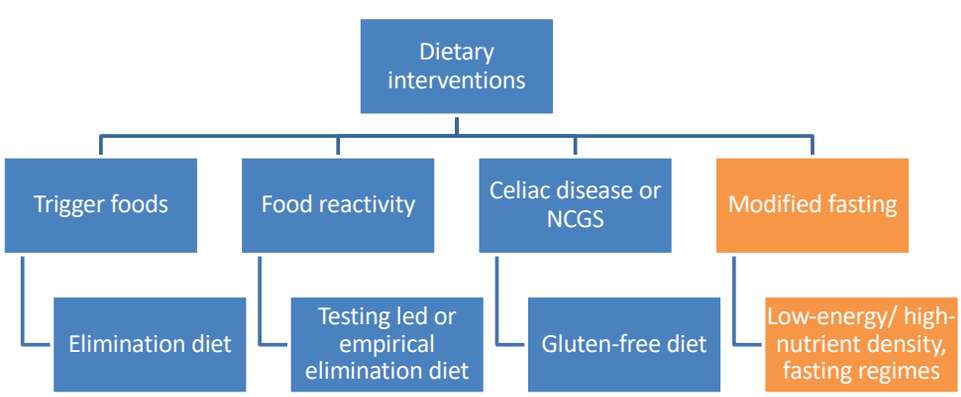
Atopic dermatitis: dietary management options



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Modified fasting

Adults received a low-energy (1085kcal/ day) density diet supplemented with high-nutrient foods such as vegetables juice, kelp, and non-refined salt to ensure high micronutrient intake. After the 6-week dietary treatment there was a significant reduction in atopic dermatitis symptoms, as well as a significant reduction in oxidative DNA damage.

J Physiol Anthropol Appl Human Sci. 2000 Sep;19(5):225-8.

Journal of PHYSIOLOGICAL ANTHROPOLOGY and Applied Human Science

Low-Energy Diet in Atopic Dermatitis Patients: Clinical Findings and DNA Damage

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Abstract Undernutrition without malnutrition (low-energy diet) increases maximum longevity, reduces the incidence of several cancers and delays their onset, in animal studies. It has also been demonstrated by experimental study that caloric restriction provides a beneficial effect on various inflammatory diseases. In this study, we offered a low-energy diet to patients with atopic dermatitis (AD). Nineteen adult patients (5 males and 14 females aged 15 to 36 years) were enrolled in the study which lasted 6 weeks. The energy intake was 55% of nutritional requirements; protein was 75%, calcium 180%, iron 130%, vitamin A 105%, vitamin C 200% and vitamin E 110% of the daily requirement. No patient experienced adverse reaction, and none dropped out of the trial. Body weight, body mass index (BMI), and systolic blood pressure had decreased significantly by the end of study. The SCORAD (scoring atopic dermatitis) index, which combines objective (extent and intensity of lesions) and subjective (daytime pruritus and sleep loss) criteria, was reduced significantly. In 11 patients with severe AD, there was a significant reduction in oxidative DNA damage. The change in the inflammatory intensity score and the change in BMI caused by energy restriction showed a significant positive correlation. The change in oxidative DNA damage levels and the change in BMI showed a positive correlation. These results clarify the relationship between weight loss and the improvement of AD. It may be hypothesized that this low-energy diet, which included several additional nutrients has a possibility to reduce inflammatory symptoms of patients with AD. *J Physiol Anthropol. 19 (5): 225-228, 2000* http://www.jstage.jst.go.jp/en/

Keywords: low-energy diet, oxidative DNA damage, atopic dermatitis

Introduction

Undernutrition without malnutrition (low-energy diet) increases maximum longevity, reduces the incidence of several cancers and delays their onset, in animal studies (Weindruch and Walford, 1982; Lee et al., 1999). It has also been demonstrated by experimental study that energy restriction provides a beneficial effect on various inflammatory diseases (Fernandes et al., 1978; Kubo et al., 1987; Ogura et al., 1989; Hishinuma et al., 1996). Moreover, in a controlled clinical trial, a low-energy diet was reported as a useful supplement to the ordinary medical treatment for patients with rheumatoid arthritis (Kjeldsen-Kragh et al., 1991).

For dietary management in patients with atopic dermatitis (AD), there are many reports concerning elimination diets that excluded foods that are statistically the most likely to be allergizing, such as cow's milk, dried soy, or eggs. On the other hand, Lüdtke et al. (1983) reported 8 cases of AD that improved by modified fasting (low-calorie vegetarian diet). However, this result did not clearly indicate the clinical effect of low-energy intake for AD. In this study, we offered a low-energy diet to 19 patients with AD, and we report clinical findings including on oxidative DNA damage, and demonstrate a relationship between weight loss and clinical improvement of AD.

Methods

Nineteen patients (5 males and 14 females aged 16 to 36 years) with AD were enrolled in the study. The mean age was 25.8 years for males and 25.0 years for females, with an overall average of 25.3 years. AD was diagnosed according to Hanifin and Rajka's criteria (Hanifin and Rajka, 1980). One patient had mild AD, with an objective

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Modified fasting

Intervention	Discussion	Guidance
Modified fasting	Modified fasting with a low-energy, high-nutrient density diet may reduce food anti-gen exposure, result in weight loss, and/or have direct anti-allergic effects.	Various approaches could be used to construct a modified fasting regime, including a daily low-energy/ high-nutrient density diet, a supervised 24-hour fast, or a daily 16-hour overnight fast.

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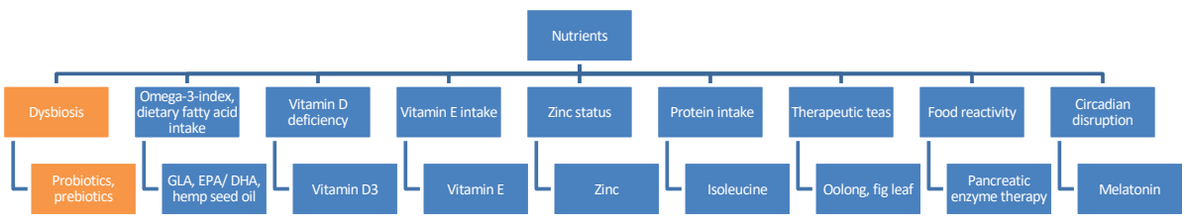
Atopic dermatitis: nutrient management options



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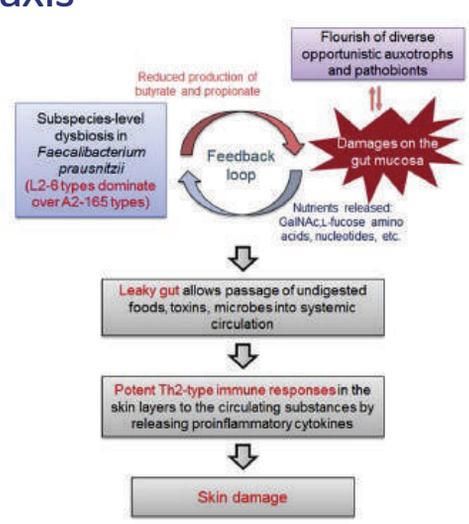
Gut-immune-skin axis

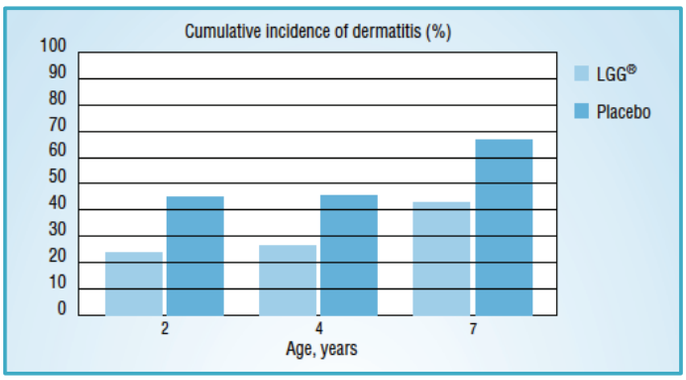


J Allergy Clin Immunol. 2016 Mar;137(3):852-60

76

Probiotics for prevention

Mothers & infants at high-risk for atopy were given *L rhamnosus* GG (10 billion daily) from 2–4 weeks prenatally to 24 weeks postnatally. The cumulative risk for developing eczema during the first 7 years of life was significantly lower in the Lactobacillus GG group than in the placebo group (42.6% vs 66.1%) in the group of children completing the 7-year follow-up.

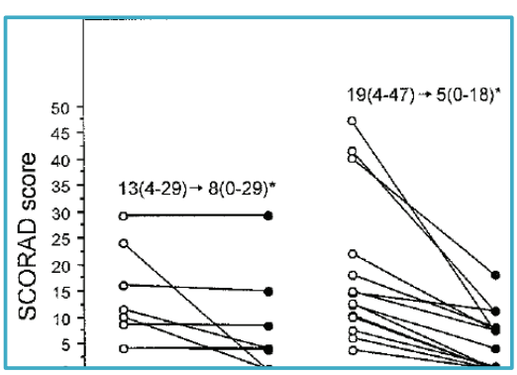


J Allergy Clin Immunol. 2007 Apr;119(4):1019-21.

77

Probiotics for pediatric treatment

Infants with atopic eczema and suspected allergy to cow's milk received *L rhamnosus* GG (10 billion daily) for around 7.5 weeks. The decrease in the SCORAD scores within the viable LGG group tended to be greater than within the placebo group.



J Pediatr Gastroenterol Nutr. 2003 Feb;36(2):223-7.

78

Probiotics for adult treatment

"Patients receiving probiotics (a combination of L salivarius LS01 and B breve BR03) showed a significant improvement in clinical parameters from baseline. The probiotics reduced microbial translocation, immune activation, improved T-helper cell (Th)17/regulatory T cell (Treg) and Th1/Th2 (P= 0.028) ratios. None of these changes were observed in the placebo group."

J Clin Gastroenterol. 2012 Oct;46 Suppl:S33-40.

PRESENTATION

Probiotics Reduce Gut Microbial Translocation and Improve Adult Atopic Dermatitis

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Background: It has been suggested that probiotics modulate atopic dermatitis (AD) progression, but no data are actually available on their mechanisms of action and on their ability to act at immune modulation in this pathology.

Objective: The aim of this randomized double-blinded active treatment versus placebo study was to evaluate clinical efficacy of an oral mix of a combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) for the treatment of adult AD patients.

Methods: Forty-eight patients were enrolled in the study (randomization ratio 2:1) and treated with a combination (LS01 and BR03) or placebo (maltodextrin) for 12 weeks. Clinical efficacy was assessed from baseline by changes in the SCORAD index and DLQI index improvement. Analysis on the gut permeability barrier, immunologic parameters, and changes in fecal microbiota and recovery of probiotics were performed at baseline, at the end of therapy, and 2 months later.

Results: Patients receiving probiotics showed a significant improvement in clinical parameters (SCORAD, $P = 0.001$ and DLQI index, $P = 0.001$) from baseline. The probiotics reduced microbial translocation ($P = 0.008$), immune activation ($P < 0.001$), improved T-helper cell (Th)17/regulatory T cell (Treg) ($P = 0.029$) and Th1/Th2 ($P = 0.028$) ratios. None of these changes were observed in the placebo group.

Conclusion: Our results suggest that this specific mixture of probiotics (LS01 and BR03 strains) may induce beneficial effects for clinical and immunologic alterations in adult AD. This combination could be considered as adjuvant therapy for the treatment of AD in adult patients.

Key Words: atopic dermatitis, probiotics, microbiota, T-helper cells, regulatory T cells

(*J Clin Gastroenterol* 2012;46:S35–S40)

Atopic dermatitis (AD) is an inflammatory and pruritic chronic relapsing skin disorder. There is direct and indirect evidence that its prevalence has increased 2- to 3-fold over the last 30 years.[1] The barrier defects in AD seem to go beyond the skin and involve the intestinal mucosa[2] where indigenous intestinal microflora contributes to the mucosal barrier function and stabilizes intestinal permeability.[3]

Probiotics were used in irritable bowel syndrome[4] and seemed to be able to modulate mucosal immune responses and reduce gastrointestinal inflammation in infants with food allergies.[5] These observations are likely to be secondary to the fact that the normal gut microflora plays a critical role in developing and maintaining normal immune functions and tolerance.[6,7]

Probiotics have additional immunomodulatory action[8] by exerting stimulatory effects on the intestinal innate and adaptive immune system,[9,10] enhancing mucosal barrier functions,[11] reducing the production of anti-inflammatory cytokines,[12] and facilitating the maintenance of immune tolerance.[13,14]

Some studies suggest that probiotics could prevent the development of atopic diseases[15,16] and might have beneficial effects in the treatment of these disorders.[17–19] These effects were not observed in all studies and, to date, probiotics cannot be recommended for treating atopic eczema.[20] The different probiotics strains used, the study designs, the characteristics of populations enrolled, and the duration of treatments may justify these contrasting results. Moreover, few studies are actually available for the adult population, despite demonstrating the positive effects of probiotics.[17–19] Thus, clinical trials are needed to evaluate the efficacy of probiotics on AD in adults and to explain their biological and immunologic mechanisms of action.

We chose the *Lactobacillus salivarius* (patented *L. salivarius* LS01 DSM 22775) strain that, in a preclinical evaluation, reduced the release of type 2 cytokines and induced an improvement in the T-helper cell (Th1/Th2) ratio.[21] Furthermore, type 2 cytokines [interleukin (IL)-4 and IL-13] play an important role in the pathogenesis of AD and dominate inflammatory milieu in atopic skin lesions by reducing filaggrin production.[22]

Bifidobacteria strains were selected, because they were present in a lesser proportion in atopic eczema infant feces[23–25] and, in particular, a supply of *Bifidobacterium breve* was found to be effective.[12] Clinical, immunologic, and microbiological parameters were evaluated before treatment, at the end of treatment and 2 months later. This aimed to assess the effectiveness of a new combination of three probiotics (LS01 and BR03).

MATERIALS AND METHODS

Patients and Study Design

Sixty adult patients suffering from AD were enrolled at the Allergy Unit of Ospedale Sacco in Milan. Forty-eight

J Clin Gastroenterol • Volume 46, Supp. 1, October 2012

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Probiotics, prebiotics

Intervention	Discussion	Guidance
Probiotics	Some probiotics have anti-allergic effects and may help in the development of oral tolerance early in life.	Probiotics are useful as both a preventative and treatment. Use of a probiotic with clinical evidence demonstrating efficacy in atopic dermatitis is important.
Prebiotics	Prebiotics support the development and restoration of the gut microbiota and, consequently, may help reduce atopy.	Prebiotics have mainly been used in formula-fed infants. If breast feeding is not possible a prebiotic should be considered.

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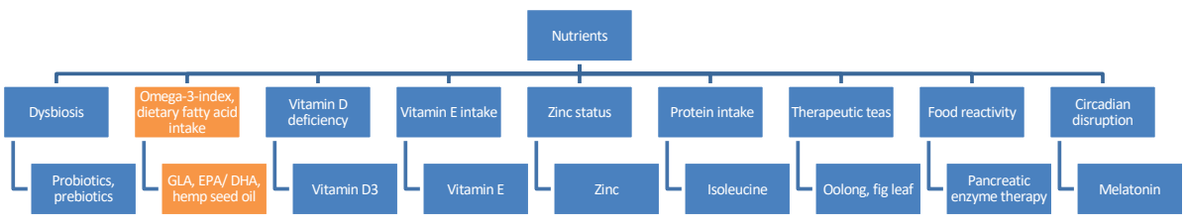
Atopic dermatitis: nutrient management options



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Fatty acids

- ✓ Evening primrose oil supplementation (2,000–6000mg/ day) for 5-months resulted in a 96% response rate and significant reduction in symptoms compared to placebo.
- ✓ Hempseed oil (30ml/ day) for 20-weeks significantly improved skin dryness and itchiness and reduced dermal medication use in adults in one study.
- ✓ Fish oil (providing at least 1.8 g omega-3 per day) for 2-4 months has generally resulted an improvement in symptoms in adults with atopic dermatitis.

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Fatty acids

Intervention	Discussion	Guidance
Fatty acids	Metabolic impairments in fatty acid metabolism, as well as dietary intakes, could affect immunological function and exacerbate atopy	Assessment of dietary intake as well as laboratory values may help direct choice of fatty acids. A trial with either omega-3 rich oils, or omega-6 rich oils alone is recommended to determine treatment response.

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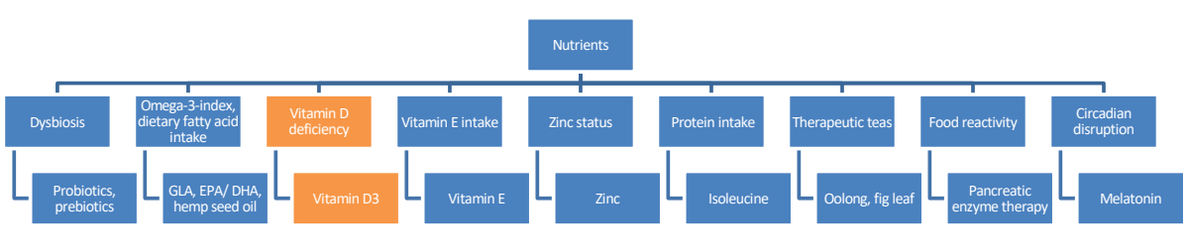
Atopic dermatitis: nutrient management options



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Vitamin D

A meta-analysis of four clinical trials, including both children and adults, showed that vitamin D supplementation reduced atopic dermatitis symptoms and clinical signs significantly when compared with placebo.

Nutrients. 2016 Dec 3;8(12).

nutrients

Article

Vitamin D Status and Efficacy of Vitamin D Supplementation in Atopic Dermatitis: A Systematic Review and Meta-Analysis

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Received: 9 August 2016; Accepted: 24 November 2016; Published: 3 December 2016

Abstract: Recent literature has highlighted the possible role of vitamin D in atopic dermatitis (AD), and that vitamin D supplementation might help to treat AD. This study determined the relationship between vitamin D level and AD, and assessed the efficacy of vitamin D supplementation. We searched the MEDLINE, EMBASE, and Cochrane databases up to May 2015. Observational studies and randomized controlled trials were included based on the available data on the serum 25-hydroxyvitamin D ([25(OH)D] level and quantified data available for severity assessed using the Scoring Atopic Dermatitis (SCORAD) index or Eczema Area and Severity Index (EASI) score. Compared with healthy controls, the serum 25[OH]D level was lower in the AD patients of all ages (standardized mean difference = −2.83 ng/mL; 95% confidence interval (CI) = −2.92 to −0.74), and predominantly in the pediatric AD patients (standardized mean difference = −3.03 ng/mL; 95% CI = −4.76 to −1.29). In addition, the SCORAD index and EASI score decreased after vitamin D supplementation (standardized mean difference = −3.85; 95% CI = −7.66 to −4.03). This meta-analysis showed that serum vitamin D level was lower in the AD patients and vitamin D supplementation could be a new therapeutic option for AD.

Keywords: atopic dermatitis; vitamin D; meta-analysis; systematic review

1. Introduction

Atopic dermatitis (AD) is a common and recurring chronic inflammatory disease characterized by pruritus and eczema. It is commonly associated with hypersensitivity to allergens, more frequently with allergic diseases such as allergic rhinitis and asthma [1]. It reportedly affects 5%–20% of children and 1%–3% adults worldwide, and its prevalence is increasing in industrialized countries [2]. The pathophysiology of AD is mainly the result of epidermal barrier dysfunctionss and immune dysregulation [1,3]. The traditional therapeutic options for AD are antihistamine and immune modulatory agents, including topical/oral corticosteroids and topical/oral calcineurin inhibitors. These classic treatments are focused on reducing skin inflammation [4], but their potential side effects and poor patient adherence indicate the importance of finding new therapeutic options. Recent studies have suggested that vitamin D supplementation may be a safe and effective alternative treatment for AD. A Cochrane review provided evidence for the efficacy of dietary vitamin D supplements as a treatment for AD in 2012 [5]. However, only two studies were reviewed, and owing to their low quality, the review could not produce conclusive evidence for the efficacy of vitamin D supplements in AD treatment.

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Vitamin D

Intervention	Discussion	Guidance
Vitamin D	Vitamin D deficiency has been associated with increased risk of atopic disease due to its immunological consequences.	Assessment of vitamin D status and subsequent supplementation in the case of deficiency. Alternatively, a routine course of vitamin D would be appropriate if deficiency is suspected.

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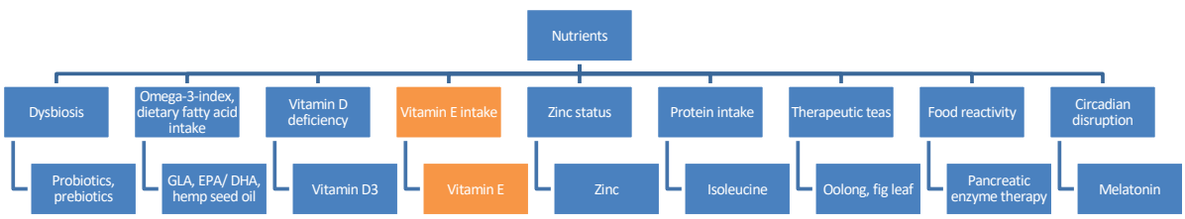
Atopic dermatitis: nutrient management options



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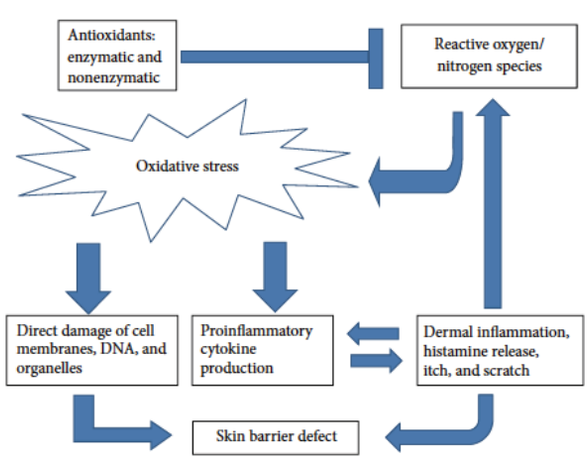
Oxidative stress



Oxid Med Cell Longev. 2016;2016:2721469.

88

Vitamin E

Vitamin E supplementation (400 IU or 268 mg of natural r,r,r-α-tocopherol in an oil base/ day) for 8-months significantly reduced subjective symptoms, with good responders showing a marked decrease in serum IgE levels.

Nutrients. 2016 Dec 3;8(12).

Report

Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels

Eroldki Tsoureli-Nikita, MD, Jana Hercogova, MD, Torello Lotti, MD, and Giovanni Menchini, MD

Abstract

Introduction

pure encapsulations

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Vitamin E

Intervention	Discussion	Guidance
Vitamin E	Vitamin appears to improve skin appearance and reduce IgE, presumably through anti-oxidant, anti-allergic effects as well as improvement of skin barrier health.	A 2-3-month course of natural vitamin E at a dose of 400 IU daily could be considered.

pure encapsulations

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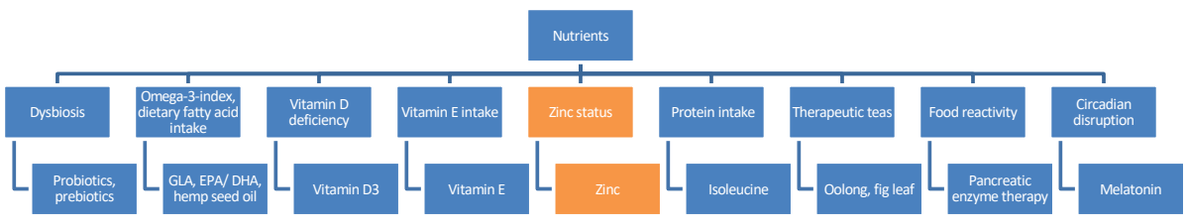
Atopic dermatitis: nutrient management options

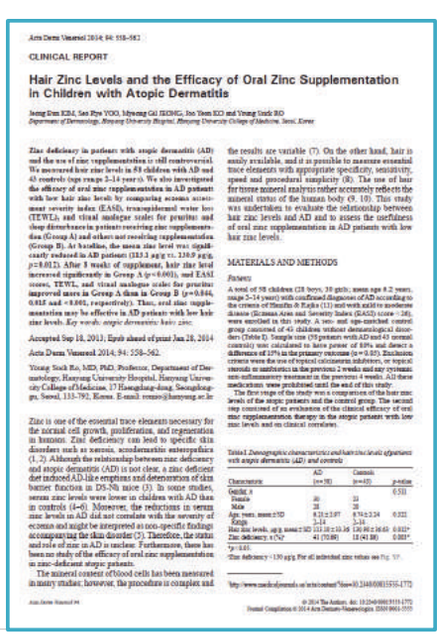


91

Zinc

Children and adolescents with atopic dermatitis and low hair zinc levels who received zinc supplementation (12mg/ day) for 8-weeks significantly improved their zinc status and reduced symptom severity. (In contrast, a clinical trial investigating the non-discriminant use of zinc found no benefit).

Acta Derm Venereol. 2014 Sep;94(5):558-62.



CLINICAL REPORT

Hair Zinc Levels and the Efficacy of Oral Zinc Supplementation in Children with Atopic Dermatitis

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Zinc

Intervention	Discussion	Guidance
Zinc	Deficiency in zinc has been associated with atopic dermatitis, however, non-discriminate supplementation was not effective.	Zinc status can be assessed with laboratory values or dietary intake. In suspected or confirmed deficiency supplementation with 10-20 mg of zinc per day is warranted.

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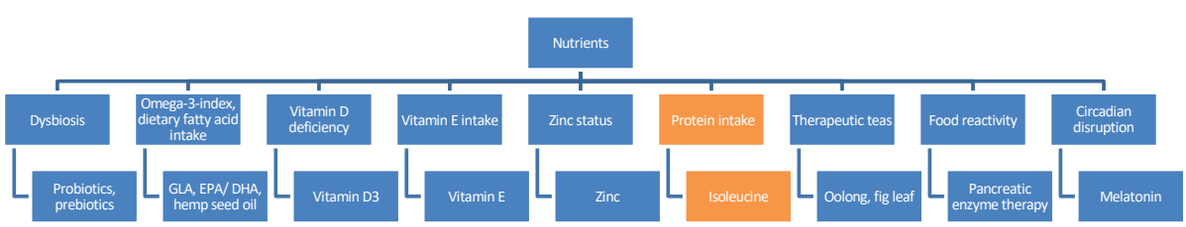
Atopic dermatitis: nutrient management options



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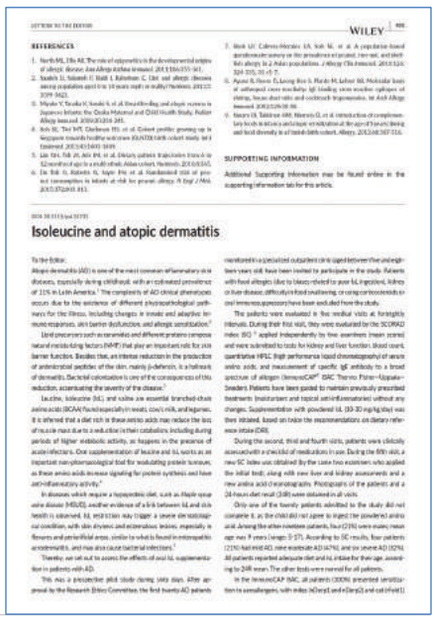
Isoleucine

In the trial 19 patients ages 5-17 were supplemented with isoleucine at a dose of 10-30 mg/kg daily for 60-days. All patients showed statistically significant clinical improvement in symptoms after supplementation with the most notable reduction in pruritus scores.

Pediatr Allergy Immunol. 2017 Aug;28(5):495-497.



WILEY

REFERENCES

SUPPORTING INFORMATION

Isoleucine and atopic dermatitis

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Isoleucine

Intervention	Discussion	Guidance
Isoleucine	Isoleucine could modify inflammation and reduce symptoms, particularly pruritis, but research is limited to a pilot study.	Consider a trial of 10-30 mg/kg daily for >60-days.

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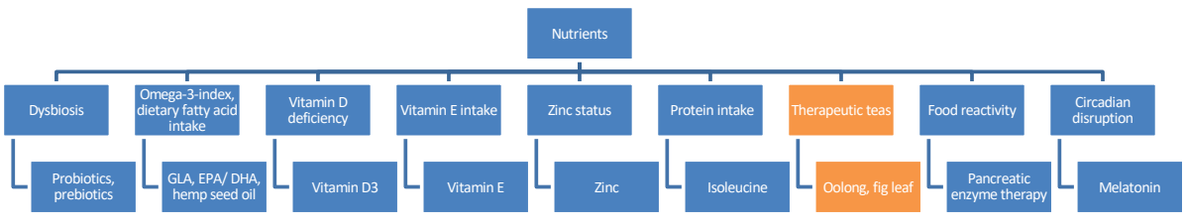
Atopic dermatitis: nutrient management options



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Oolong tea

Adults with atopic dermatitis who were instructed to drink 1 litre of oolong tea (made from a 10g teabag placed in 1000ml of boiling water and steeped for 5-minutes) between meals daily had a good clinical improvement within 1-2 weeks and maintained for at least 6-months.

Arch Dermatol 2001;137:42–43.

STUDY

A Trial of Oolong Tea in the Management of Recalcitrant Atopic Dermatitis

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Therapeutic teas

Intervention	Discussion	Guidance
Oolong tea	Unique anti-allergic properties of oolong tea make it a useful addition to nutritional therapy.	Consider 1 litre of oolong tea (made from a 10 g teabag placed in 1000ml of boiling water and steeped for 5-minutes) between meals each day.
Fig leaf tea	Fig leaf tea may modify IgE activity and alleviate symptoms.	Consider 500 ml of fig leaf tea daily. Care should be taken to use a specific fig cultivar (Grise de Tarascon) to avoid risk of photodermatitis.

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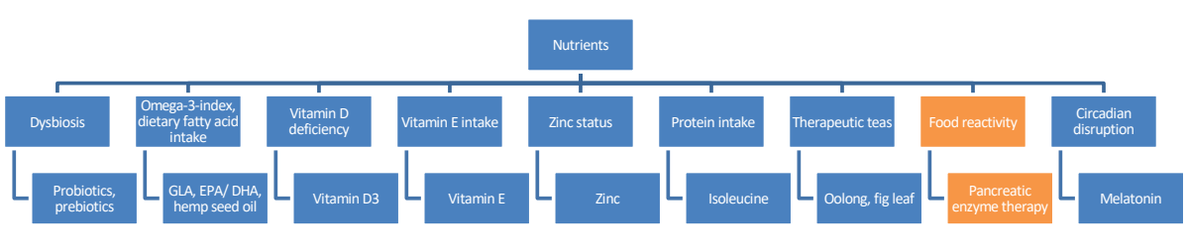
Atopic dermatitis: nutrient management options



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Pancreatic enzymes

In a clinical study of pancreatic enzyme therapy, a group of patients with severe atopic dermatitis and known food allergies who were not responding to conventional therapies or exclusion diets were administered pancreatic enzymes supplements (37,500 units of proteases with each meal and one-half of a capsule with snacks) for 6-weeks. At the end of the study patients who received the enzymes supplements had a significant improvement in atopic disease symptoms severity and a reduction in gut permeability, as measured by lactulose: mannitol ratio.

Paediatr Drugs. 2019 Feb;21(1):41-45.

SHORT COMMUNICATION

Pancreatic Enzyme Supplementation in Patients with Atopic Dermatitis and Food Allergies: An Open-Label Pilot Study

Sanford Singer[1] · Jamie Keenekoop[2] · Jonathan Meddings[3] · Julie Powell[1] · Anne Desrochers[1] · Ernest G. Seidman[4]

Abstract

Background Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects both patients and their families. Current therapies often alleviate symptoms but do not prevent or eradicate the disease.

Objectives Our objective was to determine whether pancreatic enzyme supplementation is an effective and safe treatment in refractory pediatric AD associated with food allergies.

Methods We conducted an open-label pilot study using a case-control design. Patients with severe AD and known food allergies refractory to conventional therapies and exclusion diets were recruited and treated for 6 weeks with oral supplementation of pancreatic enzymes. The primary endpoint was the severity of AD, using the Scoring Atopic Dermatitis (SCORAD) index. Secondary measures included markers of intestinal permeability (urinary sucrose and lactulose/mannitol excretion).

Results A total of 11 patients met all eligibility criteria and completed the trial. Significant improvement in AD was observed after 6 weeks of pancreatic enzyme supplementation (SCORAD index 52.3 ± 5.5 vs. 34.6 ± 7.4; $p = 0.0008$). Beneficial effect was observed in 9 of 11 patients, without adverse events. Fractional urinary sucrose excretion improved to a level comparable to that of age-matched controls ($p < 0.05$). However, urinary lactulose:mannitol ratio remained abnormally high compared with those of controls ($p = 0.01$).

Conclusions Pancreatic enzyme supplementation was associated with improved AD and gastrointestinal permeability. Additional randomized placebo-controlled studies are required before this treatment can be recommended in this clinical setting.

Key Points

Abnormal intestinal barrier function was observed in children with atopic dermatitis (AD) and food allergies, supporting the hyperpermeable gut as a contributing factor to pathogenesis.

This is the first study supporting pancreatic enzyme supplementation in patients with AD with food allergies, as pancreatic enzyme supplementation resulted in significant clinical improvement.

In addition with severe AD and food allergies, the observed association between pancreatic enzyme supplementation and improved gastrointestinal permeability is novel.

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Published online: 17 December 2018

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Pancreatic enzymes

Intervention	Discussion	Guidance
Pancreatic enzymes	Proteolytic enzymes may reduce food antigen reactivity via digestion and consequently ameliorate symptoms.	In treatment resistant patients with food reactivity, trial 37,500 units of proteases with each meal and one-half of a capsule with snacks for >6-weeks

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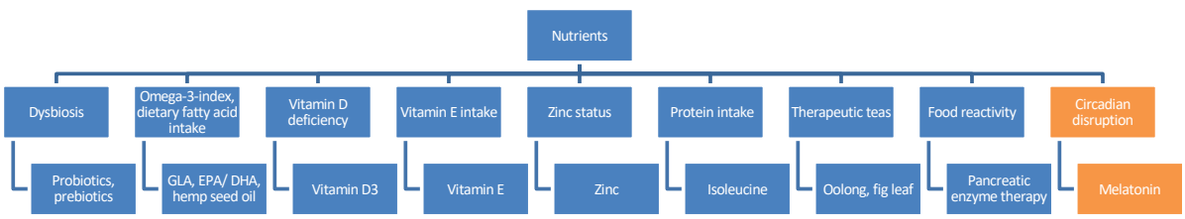
Atopic dermatitis: nutrient management options



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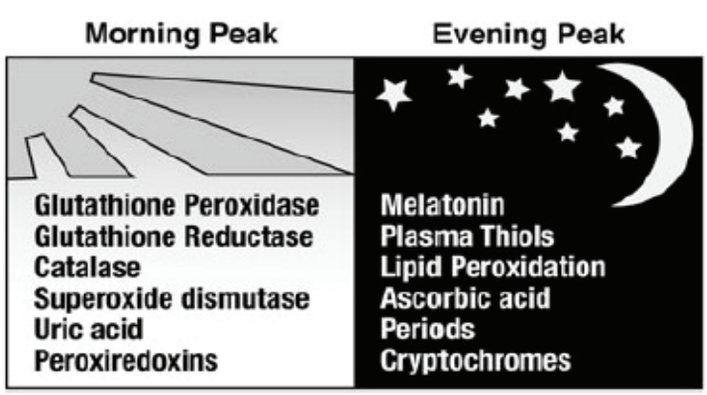
Circadian redox cycles



Antioxid Redox Signal. 2013 Jul 10;19(2):192-208.

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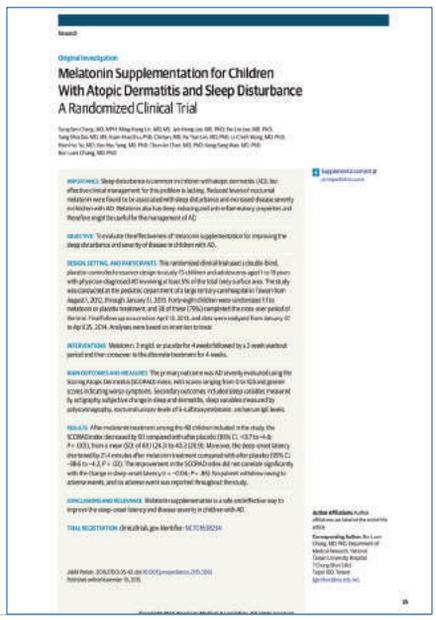
Melatonin

In children with atopic dermatitis and sleep disturbance melatonin (3 mg daily at bedtime for 4-weeks) improved sleep-onset latency and reduced disease severity.

JAMA Pediatr. 2016 Jan;170(1):35-42.



Melatonin Supplementation for Children With Atopic Dermatitis and Sleep Disturbance
A Randomized Clinical Trial

105

Melatonin

Intervention	Discussion	Guidance
Melatonin	Circadian rhythm disruption may play a role in atopic dermatitis symptom severity.	In patients with sleep disturbance, trial melatonin 3 mg daily at bedtime for >4-weeks.

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Psoriasis

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Psoriasis

"Psoriasis is a common, chronic papulosquamous skin disease occurring worldwide, presenting at any age, and leading to a substantial burden for individuals and society. It is associated with several important medical conditions, including depression, psoriatic arthritis, and cardiometabolic syndrome. Its most common form, chronic plaque or psoriasis vulgaris, is a consequence of genetic susceptibility, particularly in the presence of the HLA-C*06:02 risk allele, and of environmental triggers such as streptococcal infection, stress, smoking, obesity, and alcohol consumption."

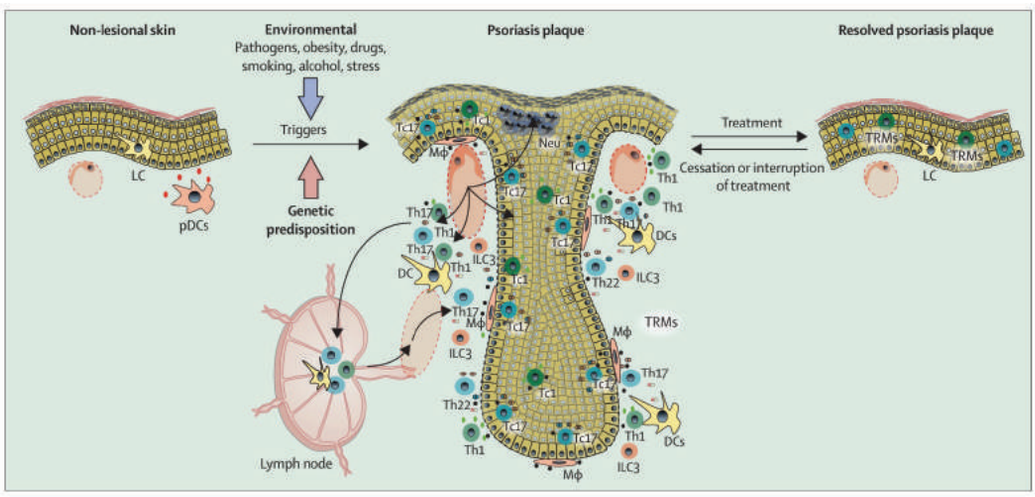
Lancet. 2021 Apr 3;397(10281):1301-1315.


Seminar

Psoriasis

108

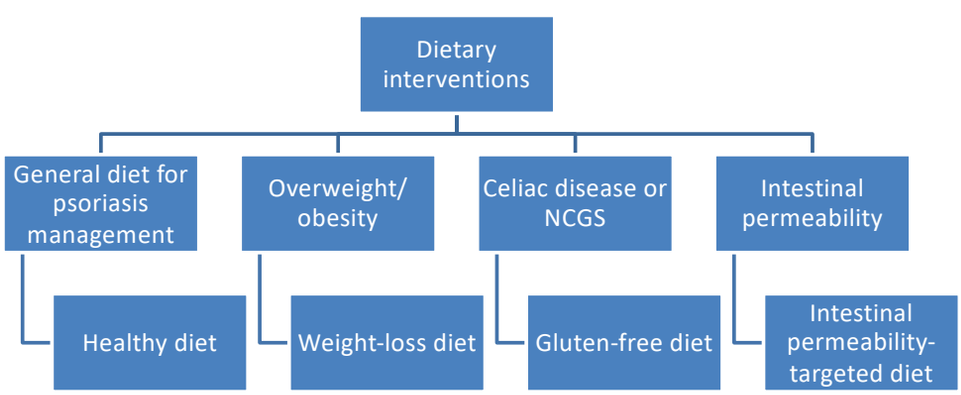
Immunopathogenesis of psoriasis and resolved psoriasis plaques



Lancet. 2021 Apr 3;397(10281):1301-1315.

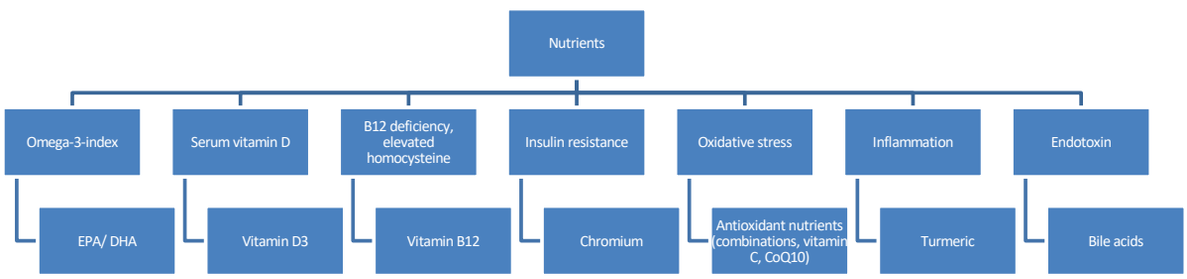
109

Psoriasis: dietary management options



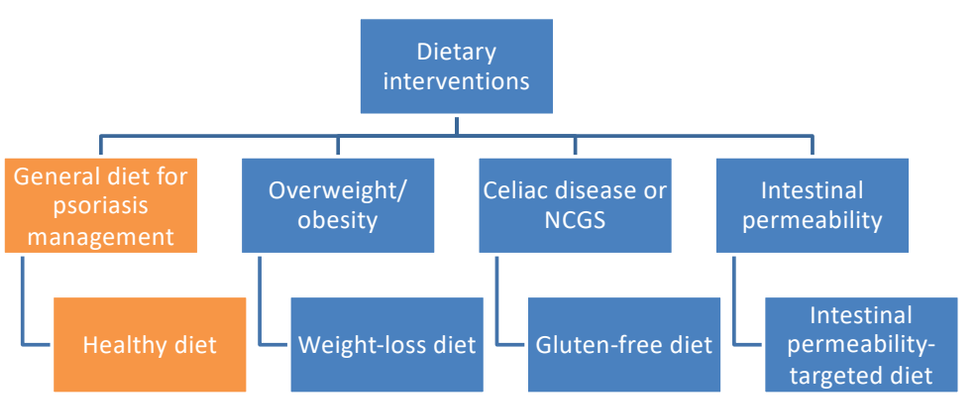
110

Psoriasis: nutrient management options



111

Psoriasis: dietary management options



112

Nutritional therapy

A woman with severe, treatment resistant psoriasis who was treated with nutritional therapy including increased vegetable intake, low consumption of meat, avoidance of junk food and sugar, and personalized nutritional supplementation experienced complete resolution of symptoms within 6-months.

Exp Ther Med. 2015 Sep;10(3):1071-1073.

EXPERIMENTAL AND THERAPEUTIC MEDICINE 10: 1071-1073, 2015

Efficacy of nutritional treatment in patients with psoriasis: A case report

ANG PENG WONG[1], TATIANA KALINOVSKY[2], ALEKSANDRA NIEDZWIECKI[2] and MATTHIAS RATH[2]

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Received August 30, 2014; Accepted June 8, 2015

DOI: 10.3892/etm.2015.2601

Abstract. Psoriasis is a chronic inflammatory skin disease characterized by thickened, silvery-scaled patches. There is currently no cure and treatments only attempt to reduce the severity of symptoms. This study reports the case of a 36-year-old female who presented to the clinic with severe psoriasis and had been treated with topical steroid creams for the past 14 years. After adherence to prescribed dietary changes for 6 months, including abundant intake of vegetables, minimal consumption of meat, and avoidance of junk food and sugar in food or drinks, as well as nutritional supplementation with Vitacor Plus, ProLysinC, VitaCfibres and LysinC Drink mix, the patient experienced complete resolution of psoriatic patches on her body.

Introduction

Psoriasis is a chronic inflammatory skin disease characterized by thickened, silvery-scaled patches. It has been associated with inflammatory and immune mechanisms probably associated with a genetic predisposition that can be triggered by stress (1,2). Psoriasis is one of the most common chronic inflammatory skin disorders, affecting ~2% of the general population (3). Psoriasis can substantially affect quality of life of patients. Numerous different treatments are available, which may allow short-term improvement and long-term control of the disease, but these measures do not cure psoriasis (4). Treatments include topical applications, systemic therapies and phototherapy; while they can be effective, a number of treatments are associated with significant adverse effects. Thus, there is a requirement for effective affordable therapies with fewer side effects that address the causes of the disorder.

Psoriasis is considered to be a T-cell-mediated inflammatory skin disease, which is characterized by hyperproliferation and poor differentiation of epidermal keratinocytes. While susceptibility to psoriasis is inherited, the disease is influenced by environmental factors, such as infections and stress (5). Diet has been suggested to be involved in the aetiology and pathogenesis of psoriasis (6,7). Fasting periods, low-energy diets and vegetarian diets have been shown to improve psoriasis symptoms in certain studies (6), and diets rich in polyunsaturated fatty acids from fish oil have also shown beneficial effects (7). These diets modify the polyunsaturated fatty acid metabolism and influence the eicosanoid profile, so that inflammatory processes are suppressed (8,7).

Case report

Written informed consent was obtained from the patient. A 36-year old female presented to the clinic with psoriasis since the age of 22. She stated that her outbreak of psoriasis originated on the scalp and slowly descended downward towards her feet. Eventually the psoriatic lesions covered a large extent of her body, with the exception of her face (Fig. 1). She had been prescribed topical steroid cream for the past 14 years. Possible cause could be due to usage of anti-dandruff shampoo (which contains coal tar) since teenage years. The patient stopped using the anti-dandruff shampoo upon the first consultation. Stopping the shampoo would not alleviate psoriasis in the time limits of the present study, but may help hasten the recovery.

At the start of treatment, the patient was advised to consume a healthy diet with abundant vegetables, minimal meat, no junk food, and to avoid taking any forms of sugar in food or drinks. The following supplements were prescribed: Vitacor Plus-1 tablet 3 times daily, ProLysinC-2 tablets 3 times daily, VitaCfibres-2 tablet 3 times daily, and LysinC Drink mix-1 scoop 4 times daily. Table I shows the list of components in these supplements. The patient was advised to stop using the steroid cream immediately at the beginning of treatment. Return appointments were scheduled once per month.

During the first month the patient experienced flaring of the skin condition with shedding of the dead skin. From the second month onwards, the psoriasis patches appeared thinner. Patches on the upper part of body (neck, shoulder, upper arms) appeared to heal faster than the lower parts of the body. This healing process continued and the psoriatic patches on the

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Healthy diet

Intervention	Discussion	Guidance
Healthy diet	Unhealthful dietary practices appear to be more frequent in patients with psoriasis and could increase disease risk and severity. Conversely, healthy dietary interventions improve the disease course.	Increasing vegetable intake, low consumption of meat, avoidance of junk food and sugar, and specific foods, such as black coffee, black tea, chocolate, pepper, smoked foods, monosodium glutamate, and alcoholic drinks may be useful. Consider dietary supplements to optimize nutritional intake and support skin health.

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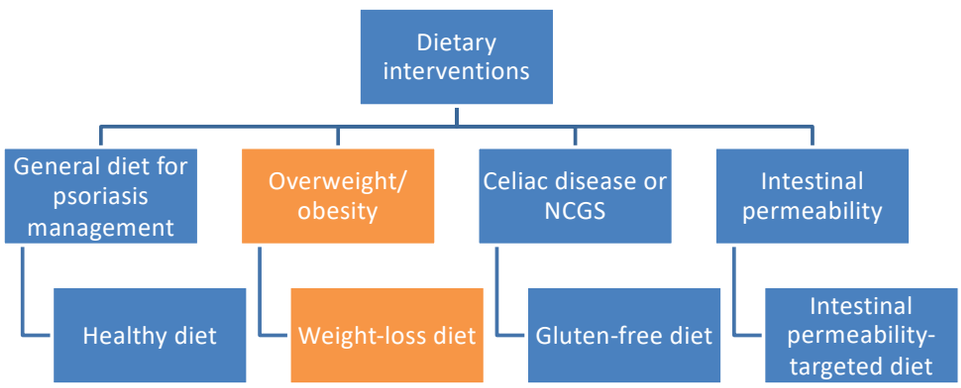
Psoriasis: dietary management options

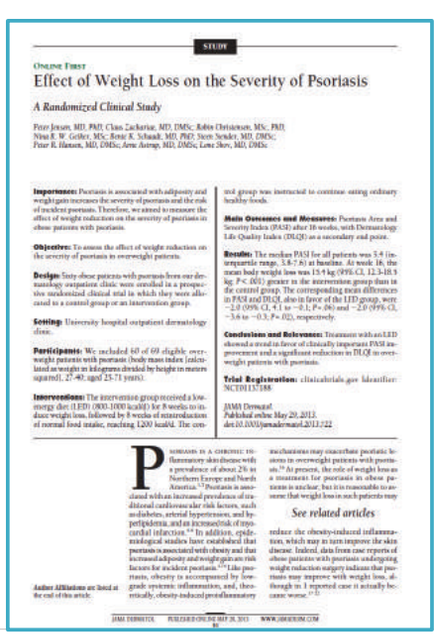


115

Weight loss

A low-energy diet providing 800-1000 kcal per for 8-weeks to induce weight loss, followed by 8 weeks of reintroduction of normal food intake, reaching 1200 kcal per day resulted in clinically important improvements in symptom and quality of life in overweight patients with psoriasis.

JAMA Dermatol. 2013 Jul;149(7):795-801.



STUDY

ONLINE FIRST

Effect of Weight Loss on the Severity of Psoriasis

A Randomized Clinical Study

Peter Jensen, MD, PhD; Claus Zachariae, MD, DMSc; Robin Christensen, MSc, PhD; Nina R. W. Geiker, MSc; Bente K. Schaadt, MD, PhD; Steen Stender, MD, DMSc; Peter R. Hansen, MD, DMSc; Arne Astrup, MD, DMSc; Lone Skov, MD, DMSc

Importance: Psoriasis is associated with adiposity and weight gain increases the severity of psoriasis and the risk of incident psoriasis. Therefore, we aimed to measure the effect of weight reduction on the severity of psoriasis in obese patients with psoriasis.

Objective: To assess the effect of weight reduction on the severity of psoriasis in overweight patients.

Design: Sixty obese patients with psoriasis from our dermatology outpatient clinic were enrolled in a prospective randomized clinical trial in which they were allocated to a control group or an intervention group.

Setting: University hospital outpatient dermatology clinic.

Participants: We included 60 of 69 eligible overweight patients with psoriasis (body mass index [calculated as weight in kilograms divided by height in meters squared], 27-40; aged 25-71 years).

Interventions: The intervention group received a low-energy diet (LED) (800-1000 kcal/d) for 8 weeks to induce weight loss, followed by 8 weeks of reintroduction of normal food intake, reaching 1200 kcal/d. The control group was instructed to continue eating ordinary healthy foods.

Main Outcomes and Measures: Psoriasis Area and Severity Index (PASI) after 16 weeks, with Dermatology Life Quality Index (DLQI) as a secondary end point.

Results: The median PASI for all patients was 5.4 (interquartile range, 3.8-7.8) at baseline. At week 16, the mean body weight loss was 15.4 kg (99% CI, 12.3-18.5 kg; $P < .001$) greater in the intervention group than in the control group. The corresponding mean differences in PASI and DLQI, also in favor of the LED group, were −2.0 (99% CI, 4.1 to −0.1; $P = .06$) and −2.0 (99% CI, −3.6 to −0.3; $P = .02$), respectively.

Conclusions and Relevance: Treatment with an LED showed a trend in favor of clinically important PASI improvement and a significant reduction in DLQI in overweight patients with psoriasis.

Trial Registration: clinicaltrials.gov Identifier: NCT01137188

JAMA Dermatol. Published online May 29, 2013. doi:10.1001/jamadermatol.2013.722

Psoriasis is a genetic inflammatory skin disease with a prevalence of about 2% in Northern Europe and North America.[1,2] Psoriasis is associated with an increased prevalence of traditional cardiovascular risk factors, such as diabetes, arterial hypertension, and hyperlipidemia, and an increased risk of myocardial infarction.[3,4] In addition, epidemiological studies have established that psoriasis is associated with obesity and that increased adiposity and weight gain are risk factors for incident psoriasis.[5,6] Like psoriasis, obesity is accompanied by low-grade systemic inflammation, and, theoretically, obesity-induced proinflammatory mechanisms may exacerbate psoriatic lesions in overweight patients with psoriasis.[7] At present, the role of weight loss as a treatment for psoriasis in obese patients is unclear, but it is reasonable to assume that weight loss in such patients may

See related articles

reduce the obesity-induced inflammation, which may in turn improve the skin disease. Indeed, data from case reports of obese patients with psoriasis undergoing weight reduction surgery indicate that psoriasis may improve with weight loss, although to 1 reported case it actually became worse.[8-12]

Author Affiliations are listed at the end of this article.

JAMA DERMATOL PUBLISHED ONLINE MAY 29, 2013 WWW.JAMADERM.COM 1

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Weight loss diet

Intervention	Discussion	Guidance
Weight-loss diet	Overweight and obesity can contribute to disease severity though increased low-grade inflammation and diet-induced weight loss results in clinical improvement.	Dietary and lifestyle-based weight loss regimes, including low-energy diets and very low carbohydrate ketogenic diets, can be considered a component of nutritional management for overweight or obese patients.

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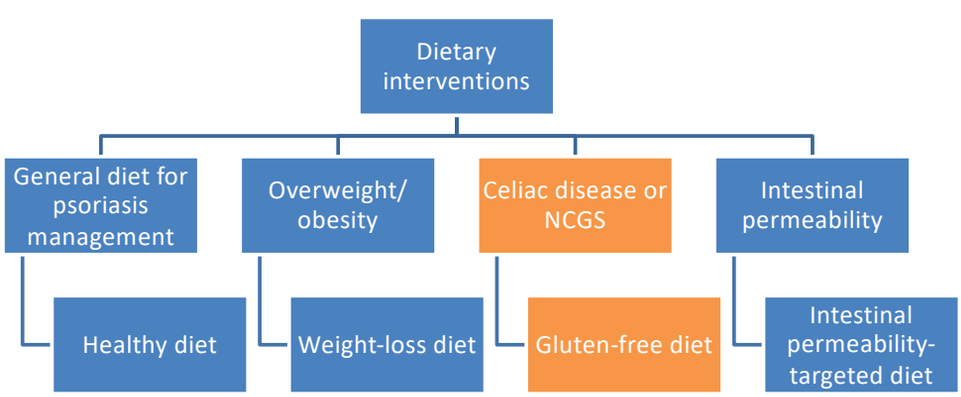
Psoriasis: dietary management options



118

Celiac disease

Coeliac screening in people with psoriasis revealed a high prevalence (4.1%) compared to controls, as assessed with anti-tissue transglutaminase antibodies and subsequently confirmed histologically. After a 6-month gluten-free diet there was a marked improvement of skin lesions in 7 out of 8 people.

Dermatology. 2015;230(2):156-60.


Dermatology

Original Paper

Association between Coeliac Disease and Psoriasis: Italian Primary Care Multicentre Study

Rudi De Bastiani, Maurizio Gabrielli, Liliana Lora, Luigi Napoli, Cesare Tosetti, Enzo Pirrotta, Enzo Ubaldi, Luciano Bertolusso, Maria Zamparella, Manuela De Polo, Cristina Nebiacolombo, Mario Bortot, Maurizio Mancuso, Paolo Bacchin, Valerio Marsala, Roberto Pinna, Antonio Tursi, Edoardo Benedetto, Alfredo Cuffari, Antonino Pati, Simona Di Caro, Gastone Perenzin, Raffaella Sala, Giacomo Calzavara Pinton, Antonio Gasbarrini

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Gluten-free diet

Intervention	Discussion	Guidance
Gluten-free diet	There is a higher frequency of celiac disease and gluten sensitivity in psoriasis, and gluten-free diets may reduce disease severity.	Confirmed celiac disease must be managed with a strict gluten-free diet, however, a gluten-free diet should be considered even in the absence of histologically confirmed celiac disease or positive antibodies i.e., non-celiac gluten sensitivity.

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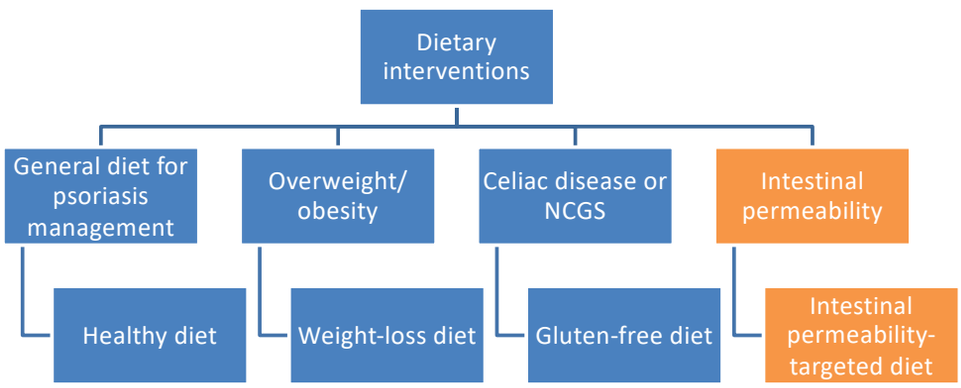
Psoriasis: dietary management options



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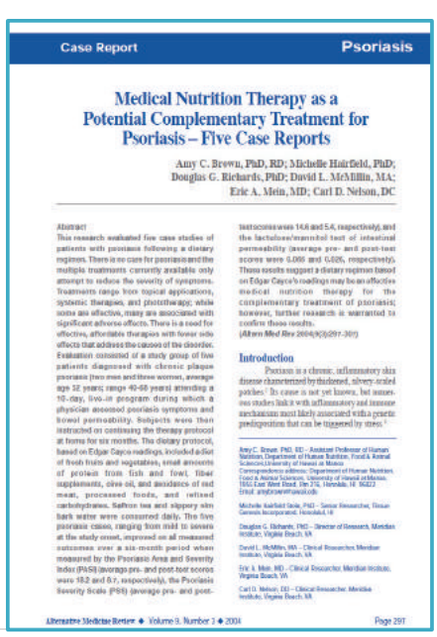
Intestinal permeability

An intestinal permeability-targeted nutritional intervention involving dietary changes (high fresh fruits and vegetables, low protein from fish and fowl, fiber supplements, olive oil, and avoidance of red meat, processed foods, and refined carbohydrates) and herbal teas (saffron tea and slippery elm bark) was found to improve psoriasis symptom scores and reduce intestinal permeability.

Altern Med Rev. 2004 Sep;9(3):297-307.


Case Report Psoriasis

Medical Nutrition Therapy as a Potential Complementary Treatment for Psoriasis – Five Case Reports

Amy C. Brown, PhD, RD; Michelle Hairfield, PhD; Douglas G. Richards, PhD; David L. McMillin, MA; Eric A. Mein, MD; Carl D. Nelson, DC

Introduction

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Intestinal permeability-targeted diet

Intervention	Discussion	Guidance
Intestinal permeability-targeted diet	Nutritional modification of intestinal permeability could benefit psoriasis, but although research is limited.	Assessment of intestinal permeability and, if indicated, a permeability-targeted nutritional intervention might be considered.

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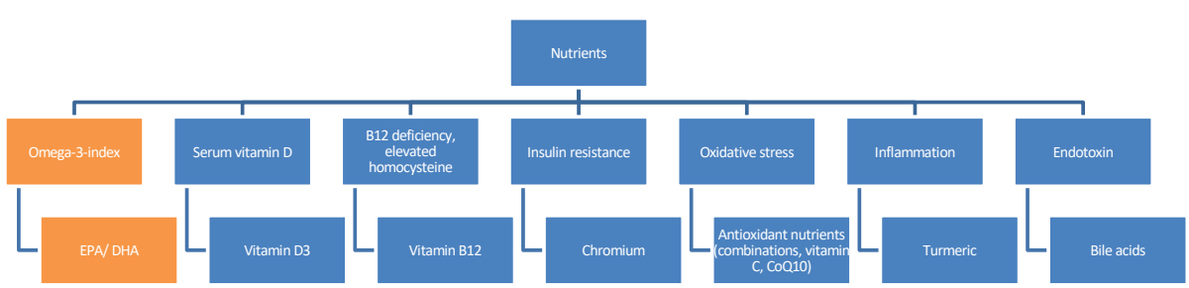
Psoriasis: nutrient management options



124

Fatty acids

A review of clinical trials evaluating fish oil for the treatment of psoriasis found moderate evidence of benefit, with 12 of the total 15 trials reviewed showing clinical benefits. Positive clinical trials have used high-dose eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily which needed to be taken for at least 6 weeks to 6 months to see improvement; typically, a range of reduction in symptom score of 40-75%.

J Am Acad Dermatol. 2014 Sep;71(3):561-9.


Reviews

Diet and psoriasis, part III: Role of nutritional supplements

125

Fatty acids

Intervention	Discussion	Guidance
Fatty acids	Both high-dose fish oil and increasing fish consumption can be effective for reducing symptoms.	Consider around 4 g EPA and/ or 2.6 g DHA or advice to consume 170 g of omega-3 rich fish daily for >6-weeks.

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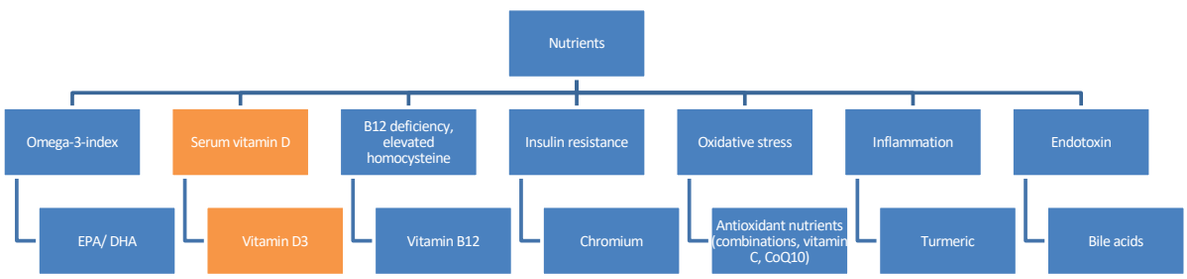
Psoriasis: nutrient management options



127

Vitamin D

"Four RCTs examined the effect of oral vitamin D supplementation on psoriasis for 173 patients and 160 patients were treated with placebo. No significant differences were found in PASI after 3, 6, and 12 months of supplementation. It is shown that 25(OH)D serum levels are significantly lower in psoriasis, but, although the granularity of RCT methodology may have influenced the pooled analysis, vitamin D supplementation did not seem to improve clinical manifestations."

Nutrients. 2023 Jul 30;15(15):3387.


nutrients

Systematic Review

Psoriasis and Vitamin D: A Systematic Review and Meta-Analysis

128

Vitamin D

Intervention	Discussion	Guidance
Vitamin D	Vitamin D deficiency may be more severe in psoriasis, and the degree of deficiency has been correlated with disease duration and severity.	Vitamin D supplementation with vitamin D3 could be considered in the presence of vitamin D deficiency.

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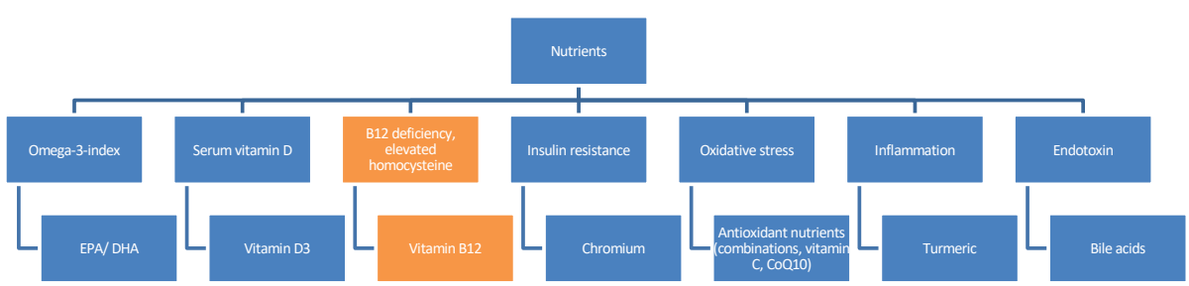
Psoriasis: nutrient management options



130

Folate, vitamin B12

Intervention	Discussion	Guidance
Folate	High-dosed folic acid and 5-methyl tetrahydrofolate (5MTHF) methotrexate as it may reduce methotrexate efficacy, while lower doses may reduce side-effects.	For patients receiving <15mg methotrexate weekly consider a dosage regime of 5 mg of folic acid per day for 2 days after the last dose of methotrexate, with an additional third dose of 5 mg on day 3 for patients receiving > 15 mg.
Vitamin B12	Vitamin B12 deficiency may exacerbate disease activity and improving nutritional status could reduce symptoms, but evidence is mixed.	It would be prudent to screen for vitamin B12 deficiency.

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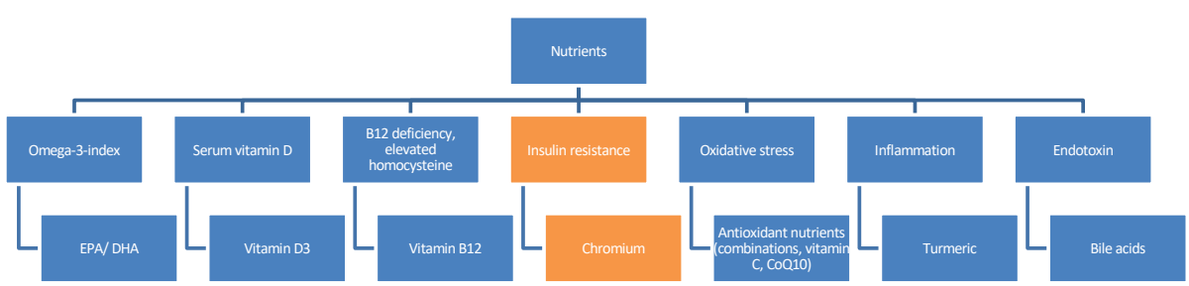
Psoriasis: nutrient management options



132

Insulin resistance

"With regard to psoriasis, we observed a significant correlation between the Psoriasis Area and Severity Index (PASI) score and insulin secretion. Moreover, the PASI score was significantly correlated with serum resistin levels—a cytokine known to be increased in insulin resistance."

Br J Dermatol. 2007 Dec;157(6):1249-51.

CONCISE COMMUNICATION

DOI 10.1111/j.1365-2133.2007.08190.x

Psoriasis patients show signs of insulin resistance

S. Boehncke, D. Thaci,* H. Beschmann,* R.L. Ludwig,* H. Ackermann,† K. Blackenhoss and W-H. Boehncke*

Summary

Correspondence

Accepted for publication

Key words

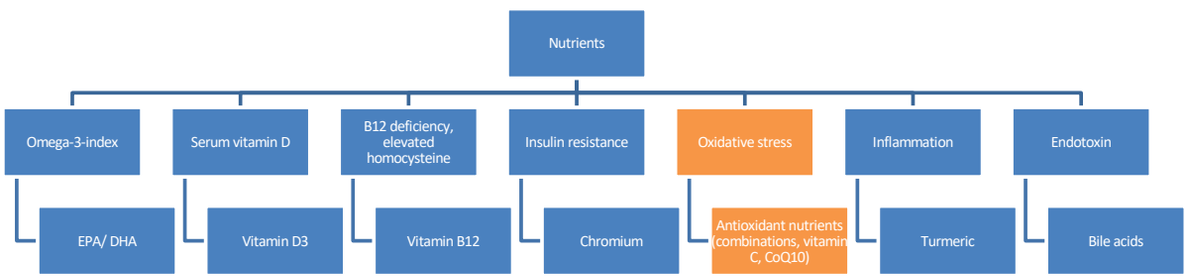
Conflicts of interest

Patients and methods

Chromium

Intervention	Discussion	Guidance
Chromium	Poor blood glucose metabolism could contribute to psoriasis in a subset of people and may be positively impacted by chromium.	Consider chromium supplementation 600 µg daily for 6-weeks in patients with established insulin resistance.

Psoriasis: nutrient management options



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Antioxidants

A clinical study of coenzyme Q10 (50 mg daily), vitamin E (natural alpha-tocopherol, 50 mg), and selenium (48 mcg) resulted in improvements several parameters related to oxidative stress, included superoxide production, copper/zinc-superoxide dismutase, and catalase, as well as a significant reduction in disease severity which correlated with normalization of the oxidative stress markers.

Nutrition. 2009 Mar;25(3):295-302.

NUTRITION

Applied nutritional investigation

Clinical and biochemical effects of coenzyme Q_{10}, vitamin E, and selenium supplementation to psoriasis patients

Zaira Kharaeva, Ph.D.*, Elena Gostova, M.D.*, Chiara De Luca, Ph.D.†, Desanka Raskovic, M.D.‡, and Liudmila Korkina, Dr.Sci.[‡,§,*]

Abstract

Introduction

Antioxidant nutrients

Intervention	Discussion	Guidance
Antioxidant nutrients	Systemic oxidative stress is a consistent feature of psoriasis and may contribute to disease development and be an important target for management.	Consider trialing a nutritional antioxidants, especially multi-nutrients formulations, CoQ10, and vitamin C.

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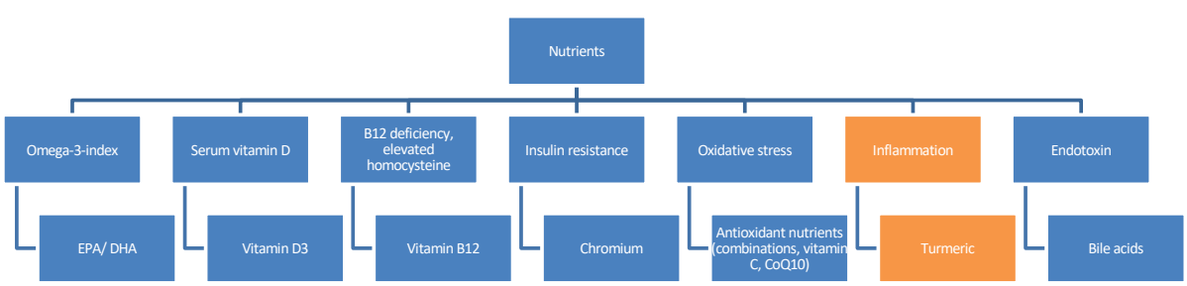
Psoriasis: nutrient management options



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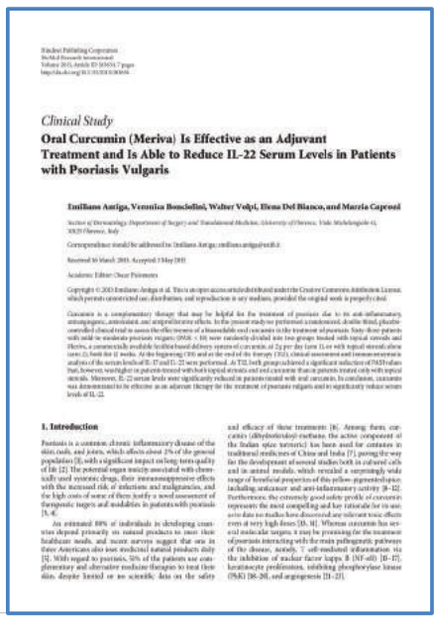
Turmeric

A trial utilizing an enhanced bioavailability formulation (Meriva; Indeena, Italy) providing 400 mg curcumin daily reduced symptoms more effectively than topical steroids alone. Moreover, IL-22 serum levels were significantly reduced in patients treated with oral curcumin.

Biomed Res Int. 2015;2015:283634.



Clinical Study

Oral Curcumin (Meriva) Is Effective as an Adjuvant Treatment and Is Able to Reduce IL-22 Serum Levels in Patients with Psoriasis Vulgaris

Emiliano Antiga, Veronica Bonciolini, Walter Volpi, Elena Del Bianco, and Marzia Caproni

1. Introduction

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Turmeric

Intervention	Discussion	Guidance
Turmeric	Turmeric extracts have shown promise as an adjuvant to standard therapy.	Consider an enhanced-bioavailability extract providing 400 mg curcumin daily.

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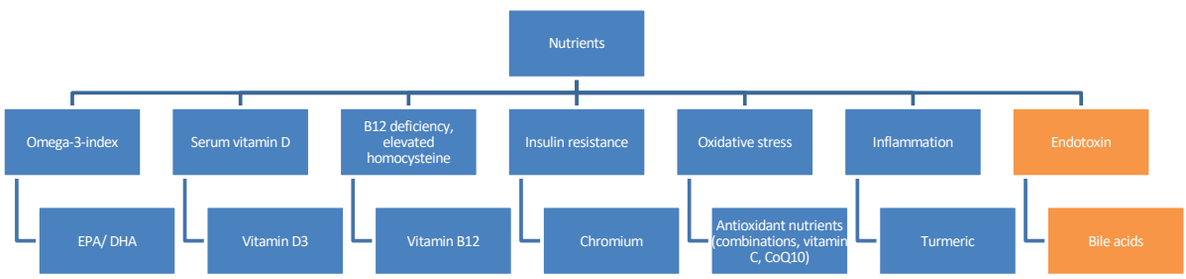
Psoriasis: nutrient management options



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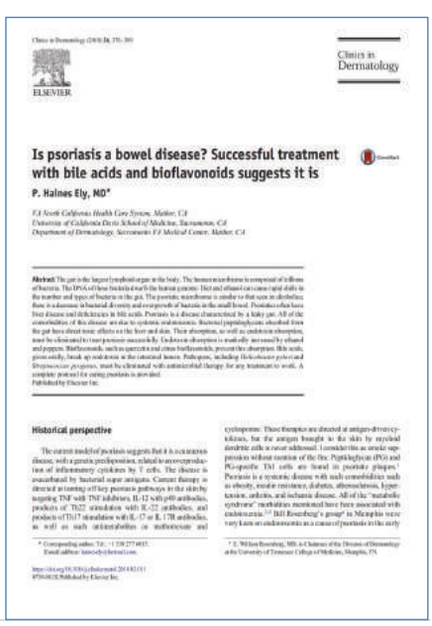
Is psoriasis a bowel disease?

"Bacterial peptidoglycans absorbed from the gut have direct toxic effects on the liver and skin. Their absorption, as well as endotoxin absorption, must be eliminated to treat psoriasis successfully. Endotoxin absorption is markedly increased by ethanol and peppers. Bioflavonoids, such as quercetin and citrus bioflavonoids, prevent this absorption. Bile acids, given orally, break up endotoxin in the intestinal lumen."

Clin Dermatol. 2018 May-Jun;36(3):376-389.


Clinics in Dermatology

Is psoriasis a bowel disease? Successful treatment with bile acids and bioflavonoids suggests it is

P. Haines Ely, MD*

Historical perspective

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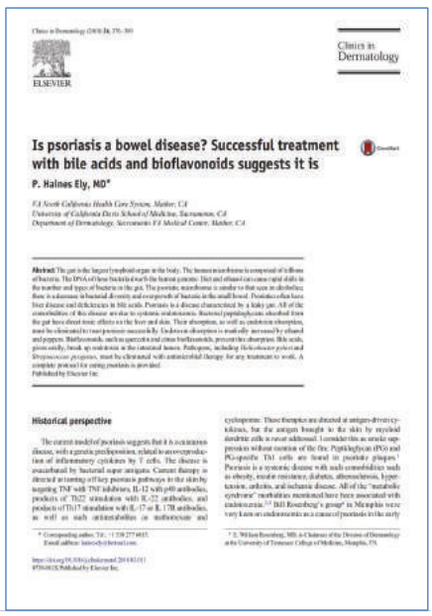
Bile acids

Bile acids have been reported to be a successful management approach for psoriasis with the primary mechanism suggested to be due to their ability to degrade gastrointestinal-derived endotoxin and prevent its systemic migration and direct adverse effects on the skin.

Clin Dermatol. 2018 May-Jun;36(3):376-389.


Clinics in Dermatology

Is psoriasis a bowel disease? Successful treatment with bile acids and bioflavonoids suggests it is

P. Haines Ely, MD*

Historical perspective

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Bile acids

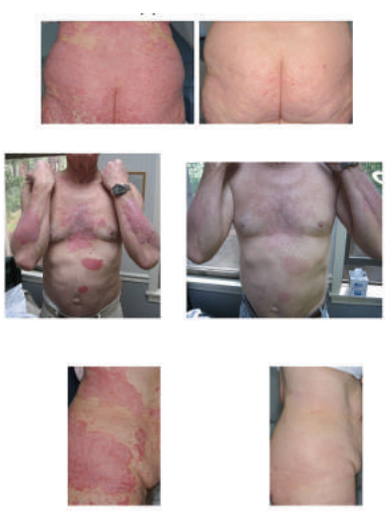

Fig. 4 Before-and-after photos of patients undertaking bile acid therapy.

Clin Dermatol. 2018 May-Jun;36(3):376-389.

144

Bile acids

Intervention	Discussion	Guidance
Bile acids	Bile acids may degrade gastrointestinal-derived endotoxin and prevent its systemic migration and direct adverse effects on the skin.	Consider bovine bile concentrate 500 mg 1-3 times daily with meals.

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Q&A

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Acne vulgaris

Acne vulgaris

Acne vulgaris is a very common skin disease with the estimated frequency of moderate-to-severe acne about 20% in the adolescent population and persisting into the 20s and 30s in around 64% and 43% of people.[1] Adult acne is more frequent in women, with an estimated prevalence of 10-12%.[2] Importantly, acne is associated with significant physical and psychological morbidity, including permanent scarring, social isolation, depression and suicidal ideation.[3]

Acne is a disease of hair follicles in the skin that are associated with an oil gland, which are known as the pilosebaceous unit. Clinically it is characterized by seborrhoea (excess grease), non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules and pustules) and scarring.[4] Lesions are most prominent where there is a high density of sebaceous glands i.e. the face (99% of cases), back (60%), and chest (15%).[5]

The pathogenesis of acne is complex and thought to involve genetic predisposition interacting with multiple factors including the action of androgens on the pilosebaceous unit, the proliferation of Propionibacterium acnes, growth factors leading to abnormal hyperkeratinization, inflammation and the induction of tissue matrix metalloproteinases and alteration of the oxidant/antioxidant ratio of the skin surface lipids.[6] [7]

Acne medications are generally classed as topical agents, systemic antibiotics, systemic retinoids and hormonal agents and are limited by adverse effects, poor compliance, and lack of cure.[8] Combination therapy with topical and oral medications for moderate to severe ace is typically utilized based on the premise they target more of the underlying pathogenic factors and improve treatment response.[9] An emerging treatment approach is nutritional therapy, which has a multi-targeted effect by simultaneously influencing multiple disease processes involved in acne pathogenesis.[10] Clinical trials have suggested an important role for nutritional interventions with evidence that dietary changes and nutritional supplementation can alter the disease pathophysiology and significantly reduce dermatological symptoms as well as related concerns including insulin resistance and mental health. Integrative use of nutritional therapy has also been shown to reduce side effects and improve efficacy of systemic retinoids.

Dietary interventions

- **Low glycemic-load diet**

The observation that a traditional diet devoid of industrialised food is associated with complete absence of acne in adolescents provided the foundation for the hypothesis that acne may be the result of diet-induced hyperinsulinemia.[11] Since this observation biological mechanisms have been explored and supported by dietary intervention studies showing that dietary therapy can reduce acne severity.

Insulin resistance is thought to play a key role in the development and pathology of acne with a primary mechanism likely to be insulin binding to insulin/ insulin-like growth factor-1 (IGF-1) receptors on keratinocytes and subsequent increased cell proliferation, in addition to the ability of insulins to stimulates the synthesis of androgens.[12] In addition, insulin-like growth factor (IGF)-1, which is typically elevated in insulin resistance and response to a high glycemic load diet, could play a role by increasing inflammation and sebum production in sebocytes.[13] Supporting an important role for insulin resistance and hyperinsulinemia patients with severe acne have been shown to have significantly higher fasting insulin levels and reduce insulin sensitivity compared to healthy

controls.[14] As proof of principle, a short term 2-week low glycemic-load (GL)/ glycemic index (GI) diet significantly reduced IGF-1 concentrations in patients with moderate to severe acne (n=66).[15]

Low glycemic-load dietary therapy and avoidance of foods that induce hyperinsulinemia may help reduce the pathological sequel of acne by restoring insulin sensitivity, and observational evidence as well as clinical trials have suggested important clinical benefits.[16] In an early observational study, 84% of patients who restricted sugar had substantial improvements or complete clearing of acne lesions after 1-month of the low-sugar diet.[17]
A clinical trial in men with treatment-resistant acne and features of insulin resistance/ metabolic syndrome found that an hypocaloric, low-glycemic load diet and an insulin sensitizing agent (metformin) for 6-months resulted in a significant improvement in acne severity.[18] A 12-week intervention with a low glycemic-load (GL) diet in males aged 15 to 25 years, with mild moderate acne found that the diet reduced acne lesions, as well as weight, free androgen index, and increased IGF-1 binding protein and the ratio of saturated to monounsaturated fatty acids of skin surface triglycerides.[19] [20] [21] A study of a 10-week low glycemic-load diet in men and women aged 20 to 27 years demonstrated a significant clinical improvement in acne lesions in addition to reduced size of sebaceous glands and decreased cutaneous inflammation.[22] A trial in which a 12-week low glycemic index and load diet was added to pharmacological treatment (topical 0.1% adapalene and oral doxycycline 100 mg daily) of men aged 18 to 25 with moderate inflammatory acne found a statistically significant reduction of inflammatory lesions (papules and pustules) in the diet group vs. controls.[23]

In contrast an 8-week low glycemic-index (GI) dietary intervention (n=43) failed to produce statistically significant differences to a high-GI comparison group, however there was a trend towards better clinical improvement on the low GL diet (acne severity score mean decrease of −26 vs. −16) with a reduction in symptom severity likely to be clinically significant to patients.[24] Similarly, a 12-week clinical trial (n=84) of topical benzoyl peroxide with or without a low-GL diet found that the low-GL diet significantly improved insulin resistance but failed to show any benefit of diet on acne symptoms. However, in this study, benzoyl peroxide treatment may have concealed the effect of diet.[25] Despite limitations in the evidence it appears that a >12-week low-glycemic load diet can reduce acne symptoms by improving metabolic health and skin physiology.

- **Acne-promoting foods**

Certain foods have been linked to the development of acne, in particular cow's milk, whey protein and cocoa, therefore limiting dietary exposure to these may be important. Several observational and case-control studies have found an association between cow's milk consumption and acne, suggesting a causal relationship.[26] [27] [28] [29] [30] [31] Whey protein has also been linked to acne development in case reports.[32] [33] [34] [35] Mechanisms underlying this connection include elevations of postprandial insulin and basal insulin-like growth factor-I (IGF-I) plasma levels with milk consumption.[36] Importantly, milk causes hyperinsulinemia despite having a low glycemic index (GI).[37] Almond and rice milks typically have a high GI and therefore may not be suitable alternatives.[38] It has also been proposed that the hyperinsulinemia effect of milk is unique to pasteurized cow's milk, and not fermented milk.[39]

Early studies investigating a link between chocolate and acne had important flaws in their design limiting the validity of conclusions that chocolate does not cause acne.[40] A more recent pilot study indicated cocoa may exacerbate acne,[41] and subsequent clinical trial found that a single-dose of pure cocoa resulted in a significant dose-response related increase in acne lesions in patients with pre-existing acne within 4-days.[42] Experimentally chocolate consumption was found to increase cytokine

release in response to *Propionibacterium* acne or *Staphylcoccus aureus*, suggesting a possible mechanism.[43]

Some dietary supplements have been associated with acne, namely vitamin B12 and Kelp. Data, mostly from case reports, suggests high dose supplementation with B12, with or without vitamin B6, in the range of 5,000-10,000 µg weekly, could exacerbate acne in some people and that acne symptoms resolve within 2-3 weeks after cessation of supplementation.[44] [45] [46] [47] Some data support a pathogenic role of B12 in acne. Lower serum vitamin B12 has been found in healthy controls vs. acne patients, and post- isotretinoin therapy.[48] [49] And B12 supplementation has been shown to increase *Propionibacterium acnes* activity, a bacterium involved in acne pathogenesis.[50]

Kelp dietary supplements have been associated with acne outbreaks in case reports.[51] [52] However, the clinical presentation does not acutely resemble Acne vulgaris. It has been proposed that iodine, of which Kelp is a rich source, could play a role in acne-pathogenesis but this is contested on the basis that there is no clear evidence that iodine itself is the problem.[53]

Nutrient interventions

- **Vitamin A**

Vitamin A was studied as a treatment for acne for decades until the synthetic vitamin A analogue isotretinoin was patented and approved for use in 1982, after which time vitamin A research for acne stopped despite no studies comparing the safety and efficacy of isotretinoin to vitamin A.[54] Because of a lack of research including a comparative clinical study it is not yet clear if there is an advantage or disadvantage of vitamin A over its synthetic apologue, but it is clear that vitamin A is significantly cheaper and much more accessible.

A review of clinical trials of vitamin A for the treatment of acne identified eight prospective studies published between 1943 and 1981.[55] Of these all the studies reported improvement apart from one study that may have been impacted by an insufficient treatment duration. The treatment response was 82%, which is similar to the clearance rate of 85% observed with isotretinoin. Dose ranges were 36,000 IU/daily to 500,000 IU/ daily, with 100,000 IU/ daily the most common. Relapse rates for vitamin A were comparable to isotretinoin (20-40%). Side effects were mostly mucocutaneous such as cheilitis and xerosis (61%), but also included pruritus (23%), transient liver enlargement (14%), epistaxis (9%), headache (7%), and alopecia (3%). Most side effects subsided during treatment or disappeared after treatment cessation. Benign elevations in triglycerides and liver enzymes occurred in some patients and returned to baseline within 2-3 weeks of stopping treatment, like those seen with isotretinoin.

A more recent case report described successful treatment of severe acne in a 14-year-old male after a 4-month course of 200,000 IU/ daily of vitamin A (with a 100,000 IU/ daily run in for the first week to assess tolerance).[56] Vitamin A treatment resulted in observable improvement within 1 month and completely eradicated cutaneous symptoms at the end of the treatment period with no relapse at 6 months post-treatment follow-up. Side effects were minimal and included dry chapped lips and redness in the face at the upper cheek/nose area, which resolved within the first 2-months of treatment.

Vitamin A toxicity, known as hypervitaminosis A, is characterized by symptoms such as dry itchy skin, desquamation, anorexia, weight loss, and headache and typically associated with intakes greater than 25, 000 IU/ daily for over 6 years and > 100,000 IU/ daily for over 6 months.[57] [58] Some of these symptoms, mostly pruritus and headache, were noted in clinical trials of vitamin A for acne, however

these were rare, mild and resolved during or after treatment. While a consensus on clinical guidelines for the safe use of vitamin A as a treatment for acne are currently lacking, those used for isotretinoin would be applicable including monitoring symptoms of adverse reactions, liver enzymes, blood lipids and pregnancy tests to avoid teratogenicity, where appropriate.

It has been estimated that a 200,000 IU dose of vitamin A would be comparable to a typical daily dose of isotretinoin.[59] With evidence that low-dose isotretinoin may be similarly effective to higher dose regimes and with fewer side-effects, it would be interesting to explore the efficacy and tolerance of lower dose vitamin A.[60] In vitamin A clinical trials marked improvement tended to occur from >100,000 IU/ daily doses with increasing effectiveness at higher doses of up to 300,000 IU/ daily and relapse increased on maintenance doses of 25,000 IU/ daily but not 50,000 IU/ daily.[61]

Based on the existing evidence vitamin A at doses of >100,000 IU/ daily for 4-months appears to be relatively safe and effective for the management of acne. A treatment duration of 4-months is considerably less than the years of continuous use associated with hypervitaminosis A, however, because the dose at which symptoms of hypervitaminosis A occurs is unclear and individual care should be taken to monitor possible side-effects.[62] [63] [64] High dose vitamin A is contraindicated in pregnancy.[65]

- **Biotin**

Severe biotin deficiency is thought to be rare, but suboptimal intakes may be common with risk factors including pregnancy, smoking, alcoholism, obesity, inflammatory bowel disease, liver disease, long-term parenteral nutrition, and use of certain medications (anticonvulsants, antibiotics) and dietary supplements (lipoic acid).[66] [67] [68] [69] [70] [71] Of relevance to acne, the medication isotretinoin reduces hepatic biotinidase activity and could increase biotin requirement.[72]

Symptoms of overt biotin deficiency include dermatological manifestations, particularly a characteristic scaly, erythematous dermatitis.[73] The rash closely resembles the acrodermatitis enteropathica of zinc deficiency, which could be in part a result of biotin dependent changes in zinc metabolism.[74] Cutaneious symptoms of biotin deficiency may also be due to changes in fatty acid metabolism.[75] Although biotin has been suggested to play a role in acne there is not yet any evidence to support an association.[76]

Biotin has been used as an adjuvant to prevent mucocutaneous side-effects of isotretinoin. In a clinical trial (n=60), biotin supplementation (10 mg/ day) was added to isotretinoin therapy over 4-months. Compared to isotretinoin alone, biotin decreased sign of hair thinning and loss (telogen and increased anagen hair rates) and maintained skin hydration.[77]

The daily intake level that constitutes an optimal amount of biotin is not yet clear, although severe deficiency is uncommon that does not mean that suboptimal intakes are not or that current recommended daily intakes reflect biotin amounts required to support health beyond preventing frank deficiency.[78] Data suggest that biotin intakes 2-3 times the current recommended intake (30 µg) may be required to optimize biotin status when there is an increased demand such as in pregnancy.[79] Clinical trials of biotin in dermatology have typically used doses of 2,500 µg to 10,000 µg daily.[80]

Biotin has no known toxicity and no adverse effects haven been reported with supplementation of 5,000 µg/ daily for 2-years or 300,000 µg/ daily for >3 months.[81] [82] Biotin supplementation can interfere with a wide variety of blood tests (immunoassays of thyroid markers, drugs, hormones,

cancer markers, cardiac function, and others) increasing risk for falsely high or falsely low results and should be stopped >48 hours prior to testing.[83]

- **Vitamin B3**

Vitamin B3 (niacin) as both nicotinamide and nicotinic acid has been used as a management approach for acne, and although both are forms of niacin and can treat vitamin B3 deficiency, they may have independent and unique pharmacological clinical effects beyond improving vitamin B3 status and so cannot be generalized as being interchangeable.[84]

Pellagra (characterized by the "3 D's" of dermatitis, dementia and diarrhea) is the classic vitamin B3 deficiency disorder, and although considered rare it may be more common than given appreciation, characterized by more diverse and / or subtle symptoms and therefore overlooked clinically. [85] Acne has been proposed to be a form of pellagra based on a new set of "3 Ds" of dermatitis (acne, seborrheic dermatitis), dyspepsia, and depression and the role of vitamin B3 in acne pathogenesis and treatment.[86] An early observational study of nicotinic acid (50 mg/ twice daily) reported that it might reduce symptoms in some patients.[87] A pilot trial of both nicotinamide (200 mg three times daily) or nicotinic acid (500 mg three times daily) with dietary changes (avoid alcohol, dairy, and a high-protein, low-fat and low-glycemic-load diet) found that although both forms of niacin were associated with improvement, nicotinic acid resulted in significantly better clinical improvements (82% vs. 73%).[88] If prescribing doses of niacin >30 mg daily patients should be made aware of flushing, a benign side effect of niacin.[89]

Nicotinamide, the amide form of nicotinic acid, has been used in dermatology because of direct anti-inflammatory effects as well as its role as a precursor for nicotinamide adenine dinucleotide, a substrate for nuclear enzyme poly-ADP-ribose polymerase (PARP-1), which repairs damage from genotoxic stresses.[90] Nicotinamide also has demonstrated a good safety profile at long-term doses of 3 g daily.[91]

An 8-week clinical trial of nicotinamide (750 mg daily), zinc (25 mg), copper (1.5 mg), and folic acid (500 mcg) reported a significant improvement in acne severity with treatment.[92] While another 8-week trial examining adjuvant use of a similar formulation (nicotinamide 600 mg, azelaic acid 5 mg, zinc 10 mg, pyridoxine 5 mg, copper 1.5 mg, folic acid 500 mcg daily) also found significant improvements in acne severity.[93]

- **Vitamin B5**

An early report suggested that high-dose pantothenic acid (10 g followed by maintenance with 1-5 g daily in divided doses) could rapidly resolve acne, with the author proposing a theory that biochemical individuality may determine greater pantothenic acid requirements in some individuals and that a relative deficiency would influence metabolism of fatty acid and steroid hormones involved in acne pathogenesis.[94] Subsequently simulated pantothenic acid deficiency was found to suppressed keratinocyte proliferation and promote differentiation.[95] And a more recent 12-week clinical study in adults with facial acne found that pantothenic acid (2.2 g daily) reduced total facial lesion count and inflammatory blemishes.[96]

- **Homocysteine lowering B vitamins**

Isotretinoin therapy for acne is associated with elevated homocysteine (theorized to be due to the inhibition of cystathionine beta-synthase by the drug and/or the drug-induced liver dysfunction) and reduced folate and vitamin B12 plasma levels, which may underlie its cardiovascular and

neuropsychiatric side effects amongst others.[97 98 99] Administration of folate and vitamin B12 with isotretinoin may prevent vitamin deficiency and correcting isotretinoin induced deficiency could reverse side effects.

A clinical trial (n=66) examining the ability of folic acid and vitamin B12 with isotretinoin to prevent hyperhomocysteinemia found that vitamin supplementation significantly decreased in homocysteine level, increased blood folate and B12 levels, and prevented decline in folate when compared to the control group (isotretinoin alone).[100] A case series of six patients with isotretinoin induced musculoskeletal pain found that treatment with folic acid and vitamin B12 reversed symptoms within 6-weeks of vitamin treatment.[101] A case report of isotretinoin induced severe vitamin B12 deficiency and painful oral aphthous-like lesions described complete healing of the ulcers within 2-weeks of discontinuing isotretinoin treatment and commencing folic acid and vitamin B12.[102]

- **Vitamin E**

A number of reports including clinical trials and anecdote from dermatology practice have suggested that vitamin E supplementation, either alone or with other vitamins (vitamin A, vitamin C) or isotretinoin, may improve acne.[103 104 105 106 107 108]

Some of these reports employed vitamin E and other vitamins to combat the oxidative and inflammatory pathophysiology now well established in acne pathogenesis.[109] Serum vitamin E has been found to be low in patients with acne.[110] Because the quality of evidence for vitamin E is limited more research is needed to determine whether vitamin E is useful for the management of acne, however, considering its relative safety and potential for benefit a course of vitamin E supplementation could be trialed.

Vitamin E has been explored for reducing side-effects of isotretinoin, which does lower serum vitamin E and increase oxidative stress. [111 112] One study suggested benefit of vitamin E (800 IU alpha tocopherol/ daily) for reducing isotretinoin mucocutaneous side-effects, in contrast two studies failed to show any benefit.[113 114 115]

- **Antioxidant nutrients**

Systemic and cutaneous oxidative stress is a feature of acne and thought to play an important role in disease pathogenesis, furthermore, nutritional antioxidant therapy is an important therapeutic consideration.[116] Studies have found important differences in systemic oxidative stress in patients with acne, in particular low blood superoxide dismutase, glutathione peroxidase (GSH-Px) and elevated malondialdehyde.[117] And the severity of serum oxidative/nitrosative stress and oxidative stress-mediated modifications of endogenous proteins has been shown to correlate with disease activity.[118]

Nutritional antioxidant therapies may help improve endogenous antioxidant defense, lower systemic oxidative stress and improve clinical symptoms. Supplementation with 200 mcg of selenium and 10 mg of vitamin E (as tocopheryl succinate) was shown to result in a good therapeutic response in acne patients with low GSH-Px at baseline.[119] And an antioxidant complex providing zinc methionine (35 mg), ascorbic acid (180 mg), mixed carotenoids (18 mg), vitamin E as D-alpha tocopheryl acetate (45 IU) and chromium picolinate (36 mcg) daily, in divided doses, resulted in a significant reduction in clinical symptoms over 12-weeks.[120] In addition to dietary supplements, improving dietary antioxidant intake with foods rich in antioxidant vitamins (especially vitamins C and E), carotenoids and polyphenols would be an important consideration.[121]

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- **Zinc**

Zinc deficiency has been found to be more frequent in patients with acne and the degree of deficiency has been associated with greater disease severity.[122] [123] [124] This may be due to zincs role in reducing inflammation, maintaining redox balance, regulation of the immune system function and androgen metabolism.[125] Zinc supplementation has a long history of use in acne, with some early studies suggesting very high-dose zinc resulting in good clinical improvements in some,[126] [127] [128] but not all studies.[129] [130]

Most studies have used zinc sulphate providing 30-150 mg of elemental zinc three times daily, and were associated with a high frequency of side-effects limiting the use of this treatment.[131] Low dose zinc gluconate (30 mg elemental zinc daily), however, was both well-tolerated and clinically effective.[132] A study assessing zinc gluconate (30mg elemental zinc) found a good clinical response with a 50% decrease in inflammatory lesions at 3 months with only a few mild gastrointestinal side-effects.[133] Because zinc may have direct disease-modifying effects zinc therapy could be useful in the absence of deficiency. Supplementation with 30 mg elemental zinc daily will minimize the probability of gastrointestinal side-effects.

Zinc may also lower isoterontin requirements. A clinical trial (n=60) comparing oral zinc sulfate (based on body weight, estimated at 18.5 mg elemental zinc daily for an 80 kg adult) plus low-dose isotretinoin and to a standard isotretinoin dose found comparable efficacy between the two groups, and no difference in relapse rates.[134] Side-effects in the zinc plus low-dose isotretinoin were significantly lower (20% vs. 76.7%). Because zinc has known synergy with vitamin A, it would be interesting for future research to explore combined use of lower dose vitamin A regimes and zinc.[135]

- **L-carnitine**

Carnitine supplementation may reduce muscular symptoms (myalgia, weakness) and elevations in liver enzymes due to isotretinoin therapy. A clinical trial (n=230) found that L-carnitine (100 mg per kg/daily) administered at the onset of muscular symptoms completely ameliorated symptoms within 5-6 days, restored serum carnitine levels, and normalised elevations in their liver enzymes.[136] The effect of carnitine on liver enzymes is consistent with a large number of clinical trials showing benefit, particularly at doses of >2,000 mg daily for > 12 weeks.[137]

- **Fatty acids**

The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) play a role in acne development, with lower serum levels linked to acne-related inflammation and clinical interventions showing good clinical responses to fish oil. The average omega-3-index, the percentage of EPA plus DHA in erythrocytes, has been found to be very low (<4%) in patients with acne and lower than the general population.[138] Suboptimal EPA/ DHA may contribute to acne pathology with serum analysis of patients with acne revealing decreased serum EPA levels and an increased pro-inflammatory state.[139] In addition to anti-inflammatory properties, omega-3 fatty acids have also demonstrated antibacterial effects relevant to acne.[140]

A series of case reports was amongst the first to demonstrate important clinical improvements on acne severity, mood and depressive symptoms with EPA (1000 mg daily) combined with zinc gluconate (15 mg), selenium (200 mcg), chromium (200 mcg) and epigallocatechin-3-gallate (200 mg) from green tea extract.[141] Subsequently, a 12-week pilot study found that fish oil (equivalent to 930 mg of EPA daily) reduced acne severity in individuals with moderate to severe acne.[142] Most

recently a 10-week, randomized controlled trial in adults with mild to moderate acne found that supplementation with EPA (1000 mg daily) and DHA (1000 mg) or gamma-linoleic acid (400mg from borage oil) found that both treatment reduced acne severity and inflammation.[143] The therapeutic effect of gamma-linoleic acid (320 mg daily) was also demonstrated in a small 12-week study.[144] Supplementation with omega-3 fatty acids (1000 mg daily) or evening primrose oil (320 mg of gamma-linoleic acid daily) also decreases mucocutaneous side effects of isotretinoin.[145] [146] [147] [148] A minimum 12-week trial course of fish oil providing around 1000 mg EPA and/ or 320 mg of gamma-linoleic acid could be considered in patients with acne.

- **Probiotics**

Alterations in the gastrointestinal microbiome been proposed to be an important factor in the development of acne and associated psychiatric morbidity with evidence to suggest that gastrointestinal disease, especially bloating, is more frequent in adolescents with acne and that alternations in gut microbiota play a role in acne pathogenesis.[149] Probiotics can modulate microbiome composition and/ or function and are emerging as a therapeutic option for improving the function of the gut-brain-skin axis with benefits likely due to their ability to reduce small intestinal bacterial overgrowth, improve dysbiosis, reduce systemic markers of oxidative stress and inflammation, and improve mental health.[150]

A clinical trial of daily lactoferrin-enriched fermented milk in adults found that the intervention resulted in significant reductions in acne symptoms and a decrease of triacylglycerols in skin surface lipids within 12-weeks.[151] Adjuvant use of probiotics (L. acidophilus, L. delbrueckii subspecies bulgaricus LB-51, B. bifidum; 30 billion CFU daily) with antibiotic therapy demonstrated that probiotic treatment enhanced symptom reduction and reduced antibiotic side effects.[152] A clinical trial of a probiotic (L. rhamnosus SP1 also known as L. rhamnosus GG; 3 billion CFU daily) in adults reduced clinical symptoms of acne and improved expression of genes involved in insulin signaling in their skin.[153] When compared to medical care alone (oral and topical medications, a vegetarian diet), the addition of a probiotic (E. coli Nissle; 5 to 50 billion CFU daily) resulted in significantly better rates of improvement or complete recovery (89% vs. 56%) of acne, papular-pustular rosacea and seborrhoic dermatitis. [154] A probiotic (*B. breve* BR03 DSM 16604, *L. casei* LC03 DSM 27537, and *L. salivarius* LS03 DSM 22776; 2 billion CFU daily) with botanical extracts (lupeol from *Solanum melongena* L. and *Echinacea* extract) significantly reduced total facial lesion count after 8-weeks, when comparted to placebo or probiotics and botanical extracts alone.[155]

A diversity of probiotics has been used to manage acne, from fermented milks to multi strain formulations. Generally, the evidence suggests probiotics, regardless of the type of product or strains used, may improve acne symptoms and complement other therapies by improving treatment outcomes. It appears prudent to trial a course of probiotics in patients with acne.

- **Green tea extract**

Green tea extract has been shown to reduce acne severity, likely because of its ability to reduce hyperseborrhea, inflammation, and anti-bacterial activity.[156] A 30-day clinical trial of an aqueous green tea extract (500 mg three times daily) found that the treatment decreased inflamed and total acne lesions in adolescents and young adults with facial acne.[157] And a 4-week clinical trial in adult women with acne found that green tea extract (providing 856mg of epigallocatechin-3-gallate daily) resulted in a statistically significant improvement in total and inflammatory acne lesions.[158] Green tea extract could be a useful approach for the treatment of adult acne. However, care should be

taken with high-doses (856mg of epigallocatechin-3-gallate) in the long-term use (several months) as this dose can raise liver enzymes and lead to adverse events in around 1% of people.[159]

- **Topical therapies**

Herbal and nutritional topical therapies that have been reported to reduice acne severity in clinical studies include 2% Wild basil (Ocimum gratissimum) essential oil,[160] 1% Copaiba (Copaifera langsdorffii Desf.) essential oil,[161] resveratrol-containing gel,[162] and seaweed-derived oligosaccharide (Laminaria digitata or kelp) and 0.1% zinc pyrrolidone.[163] The most frequently studied herbal topical treatment is 5% tea tree (Melaleuca alternifolia) essential oil, with a review of 7 clinical studies concluding that tea tree oil products reduce the number of lesions mild-to-moderate acne.[164]

Summary and Clinical Considerations

Intervention	Discussion	Guidance
Low glycemic-load diet	High-GL diets and resultant insulin resistance and hyperinsulinemia contribute to acne development, while low-GL diets may reduce acne severity.	Limit intake of high-GL foods including refined grains and sugars as well as total available sugars from carbohydrate-rich foods.
Acne promoting foods	Cow's milk, whey protein, and cocoa have been linked to the development and/or exacerbation of acne. So have dietary supplements vitamin B12 and Kelp.	Consider limiting or eliminating exposure dietary cow's milk, whey protein and cocoa if suspected to be contributing to symptoms. High dose vitamin B12 and Kelp supplements may also contribute to acne-like symptoms.
Vitamin A	Vitamin A may be a suitable alternative to isotretinoin (a vitamin A analogue).	Consider a course of >100,000 IU/ daily for 4-months. Although relatively safe, monitor for hypervitaminosis A and avoid in pregnancy.
Biotin	Biotin deficiency may be associated with acne, but more evidence is needed.	Consider >30 μg daily if risk factors for deficiency are present. Reduces mucocutaneus side-effects isotretinoin of at 10 mg daily.
Vitamin B3	Subclinical vitamin B3 deficiency may be associated with acne. Nicotinamide has pharmacological anti-inflammatory effects.	Nicotinic acid at a dose of 500 mg three times daily could be trialed, however patients should be counseled about flushing. A minimum 8-week course of 600 mg to 750 mg of nicotinamide may help reduce acne severity.
Vitamin B5	High-dose pantothenic acid has shown some evidence of benefit.	A minimum 12-week course of at least 2.2 g of pantothenic acid could be considered.
Homocysteine lowering B vitamins	Isotretinoin therapy for acne is associated with elevated homocysteine and reduced folate and	Administration of folate and vitamin B12 with isotretinoin may prevent vitamin deficiency and correcting isotretinoin

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	vitamin B12 plasma levels, which may underlie its cardiovascular and neuropsychiatric side effects.	induced deficiency could reverse side effects.
Vitamin E	Vitamin E may modulate inflammatory and oxidative stress intrinsic to acne, however, quality of evidence is limited.	Consider an empirical trial of 800 IU daily of vitamin E alone or with other antioxidants if evidence of significant inflammatory and oxidative stress.
Antioxidant nutrients	Redox imbalance and inflammation are intrinsic to acne pathophysiology, can be modulated by antioxidant nutrients and improve the disease course.	Consider multi-nutrient formulations designed to modulates oxidative stress. Improve dietary antioxidant intake with foods rich in antioxidant vitamins (especially vitamins C and E), carotenoids and polyphenols.
Zinc	Zinc deficiency is common in acne, but zinc may also have direct disease-modifying effects.	Supplementation with 30 mg elemental zinc daily would be useful in deficiency but may also be useful as a treatment in inflammatory acne independent of overt deficiency.
Carnitine	Serum carnitine is reduced by isotretinoin and carnitine replacement may offset muscular and hepatic related side-effect.	Consider acute supplementation of l-carnitine at the onset of muscular symptoms. Doses of >2,000 mg daily for > 12 weeks could be used to normalize liver enzymes.
Fatty acids	Clinical interventions have found a good clinical response to EPA and DHA and/ or GLA.	A minimum 12-week course of fish oil providing around 1000 mg EPA and DHA/ or 320 mg of GLA could be considered in patients with acne.
Probiotics	Probiotics can modulate microbiome composition and/ or function and are emerging as a therapeutic option for improving the function of the gut-brain-skin axis.	Evidence suggests probiotics, regardless of the type of product or strains used, may improve acne symptoms. It appears prudent to trial a course of probiotics in patients with acne.
Green tea extract	Green tea extract is a safe and useful intervention for reducing acne severity.	A 4-week course of green tea extract providing 856mg of epigallocatechin-3-gallate daily may be useful, but care should be taken with long-term use due to hepatic side-effects.
Topical therapies	Tea tree essential oil topical treatments have demonstrated benefits in several studies.	Topical treatment with gels and creams containing 5% tea tree essential oil can help reduce acne lesions.

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Atopic Dermatitis

Atopic dermatitis is a chronic, inflammatory skin disorder with a high prevalence, affecting 1%-20% of people worldwide including 1-3% of adults and 10%-20% of children.[1] Although more common in childhood, atopic dermatitis can persist into adulthood where it is more frequently refractory to standard treatments.[2]

The condition is characterized by chronic or chronically relapsing, eczematous, severely pruritic skin manifestations and symptoms are typically accompanied by skin barrier dysfunction, Th2 helper cell polarization, IgE elevation and autoreactivity.[3] Regulatory T cell function may also be impaired.[4] Atopic dermatitis is considered a tissue specific manifestation of a systemic 'atopic syndrome' and frequently overlaps with other atopic and inflammatory diseases.[5] Symptoms are diverse and clinical manifestations may change with age, season, psychological stress and disease severity.[6]

The pathogenesis of atopic dermatitis is known to involve interactions between environmental factors and genetic susceptibility, particularly gene polymorphisms related to immunological and epidermal barrier function. Current treatments, namely topical emollients, systemic immunosuppressants, allergen-specific immunotherapy and phototherapy, are often not adequate and have significant side effects. A better understanding of environmental factors, individual susceptibility and functional alterations may help individualize patient management and improve outcomes.[7] Clinical management should consider biological, psychological, behavioral, and dietary factors that affect disease control.[8]

Atopic dermatitis is a tissue specific manifestation of a systemic immunological disorder, the so called 'atopic syndrome,' and as such is characterized by peripheral eosinophilia and elevated IgE.[9] In support of the atopic syndrome is the association between one atopic disease and increased risk of others, in particular atopic dermatitis, asthma, allergic rhinoconjunctivitis or hay fever, and food allergy.[10] The manifestation of atopic syndrome may change over life course, a phenomena referred to as the 'atopic march,' with atopic dermatitis in infancy typically followed by allergic rhinitis and/or asthma later in life.[11]

There is a polarization of the immune system towards a T-helper 2 cell (Th2) dominant immune response in atopic dermatitis with Th2 polarization down-regulating Th1 cells and increasing production of IgE and eosinophils.[12] Pollen and food antigens are known to contribute to Th2 polarization.[13] [14]

Dysfunction of IL-10 producing T-regulatory cells, which down-regulate Th2 polarization, may also play a role.[15] Several nutritional factors may down-regulate Th2 polarization and/or improve T-regulatory cell function, including vitamin D,[16] probiotics and prebiotics,[17] and omega-3 fatty acids,[18] which may, at least in part, explain therapeutic effects of these nutrients observed in atopic dermatitis.[19]

Elevated systemic and dermal elevations in of oxidative stress are a feature of atopic dermatitis, as are increased oxidative stress during disease exacerbations and decreased endogenous antioxidant capacity.[20] For example, in patients with atopic dermatitis aged 10 to 60 years systemic lipid peroxidation assessed with malondialdehyde was increased, while antioxidant parameters including superoxide dismutase, catalase, glutathione peroxidase, glutathione, vitamin A, vitamin E and vitamin C were decreased compared to controls.[21]

Several factors may contribute to elevated oxidative stress including air pollution,[22] skin microbes including Staphylococcus aureus,[23] circadian rhythm disruption,[24] micronutrient deficiencies,[25] and

nutrient-gene interactions with genetic polymorphisms in glutathione S-transferase.[26] The antioxidants have been shown to downregulate Th2 polarization in human T cells in culture, providing a mechanism for antioxidant therapy for atopic dermatitis.[27]

Dysbiosis and increased intestinal permeability may be a contributing factor in atopic dermatitis. Compared to controls, patients with atopic dermatitis have been shown to have a preponderance of bacteria associated with gut epithelial damage, as well as low levels of butyrate and propionate.[28]

Gastrointestinal allergic and inflammatory disease has been associated with atopic dermatitis, with a high prevalence found in patients with eosinophilic gastrointestinal disorders, [29] and inflammatory bowel diseases.[30] Chronic gastrointestinal inflammation may also be an antecedent and feature of established atopic dermatitis.[31] [32] This association may be due to impaired barrier function and a subsequent increase in antigen-specific immune responses.[33] Improving gut barrier integrity would be a rational treatment approach in cases of intestinal permeability or inflammation.[34]

Exposure to air pollutants, including environmental tobacco smoke, volatile organic compounds, formaldehyde, toluene, nitrogen dioxide, and particulate matter, may increase risk for atopic dermatitis and could contribute to disease severity.[35] Exposure to cigarette smoke in particular is an important risk factor, with many studies reporting an association an association with increased atopic dermatitis prevalence.[36] And, of clinical relevance, an observational study found that children with atopic dermatitis who moved to a new daycare center with higher indoor air pollution experienced worsening of their symptoms, and that their symptoms subsequently decreased with later improvement in air quality.[37]

Psychological stress is well known to play a role in atopic dermatitis risk and symptoms flare ups, and, conversely, the disease may contribute to stigmatization, social withdrawal, anxiety and depression.[38] As an integral component of the nervous system the skin is particularly sensitive to psychological stress and immunologically responsive to stressful stimuli.[39] A blunted hypothalamus-pituitary-adrenal (HPA) axis reactivity to stress, assessed by cortisol and adrenocorticotropic hormone (ACTH) measurements, as well as an overactive sympathetic nervous system and high concentrations of catecholamine's, have been observed in patients with atopic dermatitis and may contribute to allergic inflammation.[40]

Dietary interventions

- **Trigger foods**

Identification and avoidance of trigger foods in people with atopic dermatitis and suspected food sensitivity can help to reduce symptoms. Immediate-onset (within hours) food reactions tend to be IgE mediated, while delayed-onset reactions (typically within two days) are non-IgE mediated, making elimination and re-challenge of the suspected foods the best way to identify trigger foods.[41] In a double blind placebo-controlled food challenge, 46% of children with atopic dermatitis experienced a food reaction to cow's milk, eggs, wheat or soy, with immediate-onset reactions tending to produce erythema or urticaria, and delayed-onset reactions typically producing a flare up of preexisting lesions.[42]

- **Personalised elimination diet**

Elimination diets are an important consideration in atopic dermatitis and can result in good clinical improvement, although a lack of benefit in some clinical trials has resulted in debate over their use. The failure of some studies to produce benefits, however, may be due to lack of personalization i.e.

non-discriminate elimination of foods without assessment of sensitivity. For example, a Cochrane review of 9 dietary exclusion studies found that the only study in which a clinical improvement was observed was also the only study in which food elimination was based on a suspected food allergy.[43]

Personalized elimination diets can contribute to amelioration of symptoms. In children with atopic eczema and sensitivity to eggs, confirmed by IgE antibodies, a 4-week elimination diet resulted in significant reduction in dermatitis surface area and symptom severity.[44] There was also a significant improvement in atopic dermatitis symptoms observed in young children after a 6-week elimination diet based on skin prick testing.[45] While children who received a yearlong dietary elimination program based on assessment of food allergens by skin prick and patch tests experienced an improvement in the clinical course of their atopic dermatitis, reduction in medication use, less severe allergic rash, and less gastrointestinal disorders.[46] And an elimination diet based on an IgA and IgG-dependent food sensitivity panel resulted in a mostly good or very good subjective response in children with atopic dermatitis, as well as an improved objective symptom score with elimination of particular foods.[47]

There are reports of patients with atopic dermatitis improving after removal of industrial food additives, with one study examining broad dietary elimination of food additives,[48] and another specifically eliminating monosodium glutamate.[49]

Elimination of aggravating foods can be complemented with an increase in foods that help reduce symptoms to good effect..[50]

As a precautionary note, prolonged elimination diets in young children could result in increased risk of immediate-onset and severe allergic reactions, including anaphylaxis. Evidence suggests that early introduction and continued exposure to foods is required for the development of immunological tolerance, and there are reports of people on elimination diets for cutaneous symptoms who subsequently developed more severe IgE mediated food reactions.[51] People should be made aware of possible negative consequences of long-term food avoidance and the signs and symptoms of anaphylaxis.

- **Gluten-free diet**

Celiac disease appears to be more prevalent in people with atopic dermatitis and is often clinically silent, that is, with little evidence of malabsorption or gastrointestinal symptoms despite autoantibodies and/ or biopsy-confirmed celiac disease.[52] [53] However, a gluten-free diet did not reduce atopic dermatitis severity in adults with celiac disease following a gluten-free diet for 1-year.[54] Increased IgE reactivity to food, and inhalant allergen, antigens has been reported in children with celiac disease and may be one reason why gluten restriction alone may not be effective.[55]

Non-celiac gluten sensitivity (NCGS) has not yet been well studied in relationship to atopic dermatitis but may be an important clinical consideration. Elimination diets (discussed above) frequently remove wheat, suggesting potential involvement of NCGS. In a cross-sectional study of self-reported response to elimination diets, patients with atopic dermatitis reported the best clinical improvement with wheat and gluten removal.[56] A case report described marked symptomatic improvement in a mother and her two daughters, all diagnosed with atopic dermatitis, after gluten removal. [57] Importantly, while the mother was diagnosed with celiac disease her daughters both tested negative for celiac disease. In contrast, a trial of a gluten-containing vs. gluten free diet in adult patients with atopic dermatitis found no benefit, despite improvement in gastrointestinal symptoms.[58]

- **Modified fasting**

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Modified fasting with a low-energy, high-nutrient density diet may be useful for atopic dermatitis, particularly in adults. In one study, adults received a low-energy (1085kcal/ day) density diet supplemented with high-nutrient foods such as vegetables juice, kelp, and non-refined salt to ensure high micronutrient intake. After the 6-week dietary treatment there was a significant reduction in atopic dermatitis symptoms, as well as a significant reduction in oxidative DNA damage.[59] Another study, also in adults, and using the same dietary regime, reported a striking improvement in symptoms and serological immune parameters after 2-months of treatment.[60] Supervised, short-term (24-hour) modified fasting regimes have also been used with some success.[61] [62] And a small trial (n=4) of a diet with intermittent fasting (a mostly plant based minimally processed diet and 16 hour overnight fast) suggested important clinical benefits for pruritis, overall disease severity, and quality of life.[63]

Nutrient interventions

- **Probiotics**

Some evidence suggests that that probiotics can reduce intestinal permeability, gut microbial translocation, improve immune alteration and reduce clinical symptoms in both children and adults with atopic dermatitis.[64] [65]

Probiotics may be of benefit in the prevention and treatment of atopic dermatitis, but clinical response can vary depending on patient characteristics such as age and intrinsic microbiota as well as the probiotic strain, or combination of strains, used.[66] [67]

For prevention, evidence from several clinical trials generally suggests that when probiotics are administered to pregnant mothers prenatally for 2-4 weeks and followed by treatment of the infants for the first 6-12 months of life, there is a reduction in atopic dermatitis incidence in both those at higher allergic risk and the general population.[68]

A meta-analysis of clinical studies found that the majority of evidence was for the single strain Lactobacillus rhamnosus GG, with some support for another strain of L rhamnosus and some strain mixtures.[69] Probiotics with evidence for preventing atopic dermatitis symptoms include:

- *Lactobacillus rhamnosus* GG [70]
- *Lactobacillus rhamnosus* HN001 [71]
- *Bifidobacterium bifidum* BGN4, *Bifidobacterium lactis* AD011, and *L acidophilus* AD031 [72]
- *L rhamnosus* GG, *L acidophilus* La-5, and *B animalis subsp lactis* Bb-12 [73]
- *L acidophilus* DDS-1 and *B lactis* UABLA-12 with fructooligosaccharide [74]

Importantly, some probiotics failed to show any benefit, emphasizing the importance of using an evidence-based probiotic. Clinical or immunological effects of one probiotic cannot be assumed for another probiotic, even for different strains of the same species.[75]

For treatment, probiotics can help to reduce the extent of lesions and intensity of symptoms. A meta-analysis of 25 clinical studies found that probiotics generally resulted in a significant reduction in symptoms in children and adults.[76] Analysis of specific species across these studies suggested that *Lactobacillus* and mixtures of different bacterial species showed the greatest benefit, while, conversely, treatment with *Bifidobacterium* species produced negative results. Probiotics with evidence for treating atopic dermatitis symptoms include:

- *Lactobacillus rhamnosus* GG [77]

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- *Lactobacillus salivarius* LS01 (DSM 22775) [78]
- *Lactobacillus paracasei* GMNL-133, *Lactobacillus fermentum* GM090 [79]
- *Lactobacillus sakei* KCTC 10755BP [80]

- **Prebiotics**

Prebiotics may be useful as both a preventative approach and treatment in formula-fed infants with a parental history of atopy. Human breast milk provides prebiotic oligosaccharides that help establish the infant microbiome, immune system tolerance, and prevent atopic disease, so blends of prebiotics have been developed to mimic the effects of human milk oligosaccharides on the intestinal microbiota in formula-fed infants. In a clinical study, a prebiotic mixture (90% short-chain galactooligosaccharides and 10% long-chain fructooligosaccharides/ 8 grams per liter), when given to infants for the first 6-months of life, was found to result in significant reductions in the incidence of allergic disease, including atopic dermatitis, recurrent wheezing episodes, and allergic urticaria, as well as infectious episodes, for 18-months after the intervention.[81] Additionally, a small clinical study in infants with atopic dermatitis suggested that prebiotic supplementation (kestose, a short-chain fructooligosaccharides 1-2 g/ day) for 12 weeks significantly reduced symptoms.[82]

- **Fatty acids**

There have been many studies of different fatty acids, with conflicting clinical results, however, a trial of fatty acid supplementation may be useful in some patients. Several factors may help explain differences in response to fatty acids and could aid in the identification of patients that may benefit from therapy. High steroid usage has been shown to negate the effectiveness of evening primrose oil.[83] Differences in the activity of delta-6-desaturase, an enzyme responsible for the conversion of linoleic acid to gamma-linolenic acid, are known to play a role in atopic dermatitis.[84] Individual variations in gamma-linolenic acid absorption and/or metabolism have been shown to predict treatment response to evening primrose oil.[85] Some fatty acids may have unique functional properties that influence their therapeutic effects, hemp seed oil is rich in phytonutrients for example.[86] And background dietary intake of fatty acids, as well as individual differences in metabolism, could explain why some people respond to omega-6 rich oils but not omega-3 rich oils, or vice versa.[87]

Evening primrose oil, black currant seed oil, borage oil, sunflower oil, hemp seed oil and fish oil have all been studied in atopic dermatitis. Evening primrose oil and borage oil failed to show any significant benefit in a review of 27 clinical studies.[88] However, some individual studies have demonstrated important benefits, such as a small clinical trial in children and adults with atopic dermatitis where evening primrose oil supplementation (2,000–6000mg/ day) for 5-months resulted in a 96% response rate and significant reduction in symptoms compared to placebo.[89] Similarly, a clinical trial of borage oil (500mg/ day) over 24-weeks found a clinical improvement, but only in those whom an increase in erythrocyte dihomo-gamma-linolenic acid levels was found, indicating either non-compliance or poor absorption or metabolism influenced treatment response.[90]

Hemp seed oil (30ml/ day) for 20-weeks significantly improved skin dryness and itchiness and reduced dermal medication use in adults in one study.[91] And blackcurrant seed oil (3g/day) given to mothers with a history of atopy at 8-16 weeks of pregnancy and continued throughout breastfeeding reduced risk of atopic dermatitis in infants.[92]

Supplementation with relatively high doses of fish oil (6-10g providing from 1.8g eicosapentaenoic acid up to 5.4g docosahexaenoic acid/day) for 2-4 months has generally resulted an improvement in

symptoms in adults with atopic dermatitis.[93] [94] [95] Although, one report found that fish oil made symptoms worse.[96]

- **Vitamin D**

Vitamin D status is typically low in people with atopic dermatitis, symptoms may worsen during winter months when vitamin D deficiency is more common, and restoring people to sufficiency can help reduce disease activity. A meta-analysis of four clinical trials, including both children and adults, showed that vitamin D supplementation reduced atopic dermatitis symptoms and clinical signs significantly when compared with placebo.[97]

- **Vitamin E**

Vitamin E supplementation has been shown to be a useful means to reduce the extent and severity of atopic dermatitis, including reducing itching. In one study, vitamin E supplementation (400 IU or 268 mg of natural r,r,r-α-tocopherol in an oil base/ day) for 8-months significantly reduced subjective symptoms, with good responders showing a marked decrease in serum IgE levels.[98] Subsequent studies using 400-600 IU daily for 2-4 months have also reported good treatment outcomes.[99] [100]

- **Zinc**

Zinc may be useful for atopic dermatitis when there is evidence of deficiency, in contrast zinc is unlikely to help those with adequate zinc status. Children and adolescents with atopic dermatitis and low hair zinc levels who received zinc supplementation (12mg/ day) for 8-weeks significantly improved their zinc status and reduced symptom severity.[101] In contrast, a clinical trial investigating the non-discriminant i.e., with no personalization based on zinc status use of zinc found no benefit.[102]

- **Isoleucine**

The branch chain amino acid Isoleucine has shown promise for atopic dermatitis in a pilot trial.[103] Based on the observation that isoleucine modulates inflammation and that isoleucine restriction for maple syrup disease can trigger a severe dermatological condition with skin dryness and eczematous lesions isoleucine was investigated for atopic dermatitis. In the trial 19 patients ages 5-17 were supplemented with isoleucine at a dose of 10-30 mg/kg daily for 60-days. All patients showed statistically significant clinical improvement in symptoms after supplementation with the most notable reduction in pruritus scores.

- **Oolong tea**

Oolong tea has unique anti-allergic properties, not as evident in green tea, and could be a useful addition to atopic dermatitis treatment.[104] Adults with atopic dermatitis who were instructed to drink 1 litre of oolong tea (made from a 10 g teabag placed in 1000 ml of boiling water and steeped for 5-minutes) between meals daily had a good clinical improvement within 1-2 weeks and maintained for at least 6-months.[105]

- **Fig leaf tea**

Fig leaf tea has demonstrated anti-allergic effects, specially reducing IgE interaction with its receptor on eosinophils, mast cells, and basophils.[106] An 8-week clinical trial of fig leaf tea (500 ml daily) in

patients with atopic dermatitis (n=30) found that it significantly reduced symptoms scores when compared to placebo, with the effect weakening after 4-weeks of discontinuing use.[107] During the study total IgE increased in the placebo group, but decreased in the fig leaf tea group, although differences between groups were not statistically significant. It is important to note that the fig leaf tea was prepared from a fig cultivar (Grise de Tarascon) that does not contain furanocoumarin because ingestion of fig furanocoumarins has the potential to induce photodermatitis.[108]

- **Pancreatic enzyme therapy**

Pancreatic enzyme therapy has been shown to reduce disease activity in patients with atopic dermatitis associated with food reactivity. Food allergies may play a role in atopic dermatitis, especially in patients who are resistant to standard treatments, which suggests food antigens are an important environmental factor in a subgroup of patients. [109] A first line of defense against food antigens is their digestion and subsequent inactivation.[110] At the interface between food antigens and the immune system is the gut mucosa, which normally degrades antigens but in atopic individuals is altered in a way that increases dietary antigen transfer and thus provocation of immune activation.[111] Supporting the involvement of impaired barrier function is the observation that some patients with atopic dermatitis have increased intestinal permeability.[112] And notably increased intestinal permeability has been corelated with reduced pancreatic enzyme output.[113]

In a clinical study of pancreatic enzyme therapy, a group of patients with severe atopic dermatitis and known food allergies who were not responding to conventional therapies or exclusion diets were administered pancreatic enzymes supplements (37,500 units of proteases with each meal and one-half of a capsule with snacks) for 6-weeks. [114] At the end of the study patients who received the enzymes supplements had a significant improvement in atopic disease symptoms severity and a reduction in gut permeability, as measured by lactulose: mannitol ratio.

- **Melatonin**

Circadian rhythm disruption may play a role in atopic dermatitis symptom severity and treatment with melatonin treatment showing some promise. Sleep disturbance is common in atopic dermatitis, is strongly correlated with symptom severity, and associated with lower nocturnal melatonin secretion.[115] Several factors may help restore circadian rhythm disruption including sleep hygiene, restoring natural light-dark cycles, and reducing inflammation.[116] In children with atopic dermatitis and sleep disturbance melatonin (3 mg daily at bedtime for 4-weeks) improved sleep-onset latency and reduced disease severity.[117]

- **Topical therapies**

Topical virgin coconut oil can help relieve symptoms of atopic dermatitis, an effect that may be in part due to anti-inflammatory and analgesic properties of virgin coconut oil.[118] Virgin coconut oil has also been shown to inhibit *S. aureus* from adults with atopic dermatitis in vitro.[119] Compared to mineral oil, topical application of virgin coconut oil (5ml to affected areas/ twice daily) for 8-weeeks oil was significantly better for reducing clinical symptoms and improving the health of the skin barrier, with benefits observed by the first assessment at 2-weeks and increasing with continued use.[120]

Black cumin (nigella sativa) oil may also be useful. In one study 2% black cumin ointment was as effective as betamethasone for hand eczema.[121] Black cumin is known to have potent anti-inflammatory, analgesic and anti-allergic effects, which could help explain it benefit in atopic dermatitis.[122]

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Summary and Clinical Reference

Intervention	Discussion	Guidance
Trigger foods	Foods that trigger symptoms are relatively common but often overlooked, and avoidance may help control symptoms.	Trigger foods can be identified based on patient history; however, people may not have previously associated foods with a flare up in their symptoms. Routine elimination and re-challenge with cow's milk, egg, wheat or soy may be useful. Re-challenge in a medical setting may be advise if there is risk of anaphylaxis.
Personalized elimination diet	Elimination diets can help reduce symptoms by limiting exposure to allergenic foods that are exacerbating atopy.	An elimination diet can be based on food sensitivity testing, including IgG. Without testing, an elimination and re-challenge with major and/ or suspected food allergens may still be useful. Reducing exposure to food additives and MSG may be useful.
Functional foods	Advice to increase intake of foods with anti-allergic, anti-inflammatory effects such as antioxidant and omega-3 fatty acids rich-foods has been shown to complement an elimination diet.	Advise patient to increase intake of polyphenol-rich fruits and vegetable foods and beverages, additionally increase intake of omega-3 rich foods such as nuts, seeds, and fish.
Gluten free diet	Celiac disease and NCGS may be associated with atopic dermatitis, and a gluten-free diet may be supportive.	Screen for celiac disease due to higher prevalence in atopic dermatitis. Consider NCGS and a gluten-free diet.
Modified fasting	Modified fasting with a low-energy, high-nutrient density diet may reduce food anti-gen exposure, result in weight loss, and/or have direct anti-allergic effects.	Various approaches could be used to construct a modified fasting regime, including a daily low-energy/ high-nutrient density diet, a supervised 24-hour fast, or a daily 16-hour overnight fast.
Probiotics	Some probiotics have anti-allergic effects and may help in the development of oral tolerance early in life.	Probiotics are useful as both a preventative and treatment. Use of a probiotic with clinical evidence demonstrating efficacy in atopic dermatitis is important.
Prebiotics	Prebiotics support the development and restoration of the gut microbiota and, consequently, may help reduce atopy.	Prebiotics have mainly been used in formula-fed infants. If breast feeding is not possible a prebiotic should be considered.

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Fatty acids	Metabolic impairments in fatty acid metabolism, as well as dietary intakes, could affect immunological function and exacerbate atopy	Assessment of dietary intake as well as laboratory values may help direct choice of fatty acids. A trial with either omega-3 rich oils, or omega-6 rich oils alone is recommended to determine treatment response.
Vitamin D	Vitamin D deficiency has been associated with increased risk of atopic disease due to its immunological consequences.	Assessment of vitamin D status and subsequent supplementation in the case of deficiency. Alternatively, a routine course of vitamin D would be appropriate if deficiency is suspected.
Vitamin E	Vitamin appears to improve skin appearance and reduce IgE, presumably through anti-oxidant, anti-allergic effects as well as improvement of skin barrier health.	A 2-3-month course of natural vitamin E at a dose of 400 IU daily could be considered.
Zinc	Deficiency in zinc has been associated with atopic dermatitis, however, non-discriminate supplementation was not effective.	Zinc status can be assessed with laboratory values or dietary intake. In suspected or confirmed deficiency supplementation with 10-20 mg of zinc per day is warranted.
Isoleucine	Isoleucine could modify inflammation and reduce symptoms, particularly pruritis, but research is limited to a pilot study.	Consider a trial of 10-30 mg/kg daily for >60-days.
Pancreatic enzymes	Proteolytic enzymes may reduce food antigen reactivity via digestion and consequently ameliorate symptoms.	In treatment resistant patients with food reactivity, trial 37,500 units of proteases with each meal and one-half of a capsule with snacks for >6-weeks
Melatonin	Circadian rhythm disruption may play a role in atopic dermatitis symptom severity.	In patients with sleep disturbance, trial melatonin 3 mg daily at bedtime for >4-weeks.
Oolong tea	Unique anti-allergic properties of oolong tea make it a useful addition to nutritional therapy.	Consider 1 litre of oolong tea (made from a 10 g teabag placed in 1000ml of boiling water and steeped for 5-minutes) between meals each day.
Fig leaf tea	Fig leaf tea may modify IgE activity and alleviate symptoms.	Consider 500 ml of fig leaf tea daily. Care should be taken to use a specific fig cultivar (Grise de Tarascon) to avoid risk of photodermatitis.
Topical therapies	Topical virgin coconut oil has anti-inflammatory,	It is important to use virgin coconut oil, as processing removes bioactive unique to

	analgesic and anti-bacterial effects, in addition to improving skin health.	virgin oil. Apply to affected areas twice daily. Black seed oil and/or ointment may also be effective.

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Psoriasis

Psoriasis

Psoriasis, a chronic inflammatory multi organ disorder with clinical manifestation in the skin and often the joints, is very common with an estimated prevalence of approximately 2%–5% of the population.[1] It is typically characterized by raised, well-demarcated, erythematous oval plaques with adherent silvery scales and is associated with significant comorbidity including depressive illness, cardiovascular disease, psoriatic arthritis, and decreased quality of life.[2]

Although classically considered an autoimmune disorder, psoriasis can move across a spectrum of autoinflammation to autoimmunity. In contrast to autoimmunity, autoinflammation is characterized by systemic inflammation in the absence of high-titer autoantibodies or autoreactive T lymphocytes.[3] This spectrum may help explain the progression of psoriasis from an IL-1–TNF-mediated, neutrophil-dominated inflammation (innate autoinflammatory response) that initiates a Th17/Th22-dominated early T-cell infiltrate that turns into a Th1-dominated psoriasis plaque (adaptive autoimmune response).[4]

Chronic inflammation can contribute to the development of psoriasis as well as comorbidities and metabolic disease risk and is thus an important therapeutic consideration. Psoriasis shares immunological pathways with other chronic inflammatory disease, including arthritis, obesity and other autoimmune diseases.[5] However, there are also distinct differences in the immunopathology, suggesting unique management strategies are needed.[6] Dysregulation of both innate and adaptive immune systems are involved in psoriasis, and is uncertain if psoriasis is primarily an autoimmune disease or an inflammatory disorder that evolves into an autoimmune disease.[7]

Polarization of Th1 and low Th2 cells is thought to be central to psoriasis, however it appears both Th1 and Th2 are involved in psoriasis pathogenesis.[8] Other important mediators of inflammation in psoriasis are IL-23,[9] IL-17,[10] and adipokines including adiponectin.[11] Inflammatory pathways are important targets for nutritional interventions,[12] which may have dual benefit of addressing inflammatory comorbidities and reducing metabolic disease risk.[13] As an adjuvant therapy, curcumin, for example, has been shown to reduce inflammation and improve treatment outcome.[14] C-reactive protein (CRP) correlates with disease severity and may be useful for monitoring nutritional intervention response.[15]

Dysbiosis of gut bacteria is thought to play a primary role in the development and perpetuation of autoimmune diseases, and it is well established that the gut microbiota can influence the expression specific lymphocyte subsets involved in autoimmunity.[16] Psoriasis shares genetic and clinical relationships with Cohn's disease, which is linked to gastrointestinal dysbiosis and loss of tolerance to intestinal microbes, and it has been proposed that psoriasis is linked to dermal dysbiosis and loss of tolerance to skin microbes.[17]

Although intestinal dysbiosis has not been well studied in psoriasis, an experimental study has suggested it could be an initiating factor in systemic Th17 activation and psoriasis-like skin inflammation.[18] Intriguingly, probiotic administration to people with psoriasis has been shown to reduce systemic inflammation.[19] And a case study of an adult man with treatment refractory psoriasis reported dramatic normalization of his psoriasis after H. pylori eradication for gastroduodenitis, despite no previous clinical symptoms indicating gastrointestinal involvement.[20]

Psychological stress and alterations in sympathetic adrenal medullary axis and hypothalamic pituitary adrenal (HPA) axis function share a bi-directional relationship with psoriasis, the so called brain-skin axis.[21] On one hand psoriasis itself is a cause of significant psychological stress, while on

the other psychological stress could contribute to the development and exacerbation of psoriasis though neurogenic inflammation, including interactions with leucocytes and mast cells.[22]

Stressful life events have been linked to subsequent psoriasis exacerbations,[23] and there is a clinically significant prevalence of depression, anxiety and perceived stress.[24] While features of HPA axis dysfunction in psoriasis include significantly higher HPA axis reactivity to acute stress,[25] hypocortisolism,[26] and evening elevations in cortisol. [27] Cortisol expression and HPA axis dysfunction have been shown to correlate with psoriasis severity.[28] [29] Mind body interventions have some evidence to suggest they can improve quality of life and reduce feelings of stress as well as disease severity in people with psoriasis, especially cognitive behavioral therapy.[30]

Comorbid illnesses are an important consideration in psoriasis, which is associated with several systemic disorders, including Crohn's disease, type-2 diabetes mellitus, cardiovascular disease, metabolic syndrome, depression, and cancers, particularly lymphoma and skin cancer.[31] Notably, between 6 to 42% of patients with psoriasis have psoriatic arthritis.[32] These associations suggest that psoriasis may be the cutaneous manifestation of a systemic inflammatory state.[33]

Standard drug, topical and phototherapy treatments for psoriasis frequently have adverse side effects and suffer from inadequate efficacy, thus safer and more effective management options are needed.[34] An improved clinical approach to the management of psoriasis could include individualized, patient-centered care in addition to addressing modifiable environmental and nutritional factors as these play an important role in the both the development and perpetuation of the disease. [35] [36]

Dietary interventions

- **Healthy diet**

Several factors associated with unhealthful diets have been found to be common in people suffering from psoriasis, including a higher consumption of simple carbohydrates, total fat lower intake of complex carbohydrates, omega-3 PUFA, and fiber, some of which correlated with disease severity.[37] An observational study found that a greater degree of adherence to a traditional Mediterranean-style diet was associated with lower severity of psoriasis symptom scores and inflammation, as assessed by CRP.[38]

In an intervention study most patients with psoriasis (88.37%) reported reduced scaling and erythema, milder outbreaks during the year, and improved quality of life with advice to increase consumption of beta-carotene containing foods, fruit, white meat and whole grains and decrease specific foods, such as black coffee, black tea, chocolate, pepper, smoked foods, beef, monosodium glutamate, and alcoholic drinks.[39] And a woman with severe, treatment resistant psoriasis who was treated with nutritional therapy including increased vegetable intake, low consumption of meat, avoidance of junk food and sugar, and personalized nutritional supplementation experienced complete resolution of symptoms within 6-months.[40]

- **Weight loss diet**

Overweight and obesity, especially central obesity, may play an important contributory role to the development and exacerbation of psoriasis and nutrition-based weight loss plan could be considered as it has been shown to reduce symptoms.[41] Several clinical studies have found that dietary and lifestyle weight loss intervention reduce the severity of psoriasis in overweight or obese people.[42]

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A low-energy diet providing 800-1000 kcal per for 8-weeks to induce weight loss, followed by 8 weeks of reintroduction of normal food intake, reaching 1200 kcal per day resulted in clinically important improvements in symptom and quality of life in overweight patients with psoriasis.[43] Another investigation found that a low-energy diet, providing 855 kcal per day and mostly comprised of fresh and cooked vegetables, resulted in a significant reduction in serum lipids and clinical symptoms of psoriasis after 4-weeks.[44] A low-energy diet that was also designed to increase omega-3 (average 2.6 grams per day) and reduce omega-6 polyunsaturated fatty acid intake improved metabolic profile, improved response to immuno-modulating therapy, and resulted in a significant clinical improvement over 6-months.[45] A 2-phase rapid weight loss diet (4-weeks of a ketogenic diet followed by 6-weeks of a balanced, hypocaloric, Mediterranean-like diet) in overweight or obese adults with chronic plaque psoriasis resulted in a mean body weight reduction of 12.0% (-10.6 kg) and significant improvements in psoriasis symptom scores (≥50% and ≥75% in 97.3% and 64.9% of patients, respectively), body surface area involved (-17.4%) and an improvement in itch severity and quality of life.[46] A comparison of a ketogenic diet to a Mediterranean-style diet in patients with obesity and psoriatic arthritis indicated superiority of the ketogenic diet for reduction of inflammatory markers of inflammation and disease activity.[47]

- **Gluten-free diet**

Both celiac disease and non-celiac gluten sensitivity (NCGS) have been associated with psoriasis, and a gluten-free diet has been shown to reduce symptom severity in some cases.[48] It has been estimated that people with psoriasis have an approximately 3-fold increased risk of celiac disease.[49] Although most investigations have implemented gluten-free diets in antibody-positive psoriasis patients, antibodies to gliadin may be elevated in the absence of biopsy-confirmed celiac disease,[50] and improvements in manifestations similar to psoriasis have been observed in people with NCGS after a gluten-free diet.[51] These observations suggest that the possibility of gluten sensitivity should be considered even in the absence of histologically confirmed celiac disease or positive antibodies.

Clinical studies and case reports have demonstrated important benefits of gluten-free diets in psoriasis patients with gluten sensitivity.[52] [53] [54] In one such study, coeliac screening in people with psoriasis revealed a high prevalence (4.1%) compared to controls, as assessed with anti-tissue transglutaminase antibodies and subsequently confirmed histologically. After a 6-month gluten-free diet there was a marked improvement of skin lesions in 7 out of 8 people.[55] Another report comparing the effects of a gluten-free diet in psoriasis patients with and without positive antibodies found that there was a highly significant decrease in psoriasis symptoms scores, but only in those with positive antibodies.[56]

- **Intestinal permeability-targeted diet**

Increased translocation of gut-derived endotoxin into the peripheral circulation has been suggested to play a role in the development of dermatological disorders.[57] Indeed, metabolic endotoxemia associated with intestinal permeability is a well-established source of chronic low-grade inflammation.[58] There is evidence of increased intestinal permeability in patients with psoriasis compared to healthy controls.[59] A case series utilizing an intestinal permeability-targeted nutritional intervention involving dietary changes (high fresh fruits and vegetables, low protein from fish and poultry, fiber supplements, olive oil, and avoidance of red meat, processed foods, and refined carbohydrates) and herbal teas (saffron tea and slippery elm bark) reported improvement in psoriasis symptom scores and reduced intestinal permeability.[60] The complex nature of a dietary intervention makes it hard to attribute symptomatic benefit specifically to modification of intestinal permeability, more research is needed to support this hypothesis.

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Nutrient interventions

- **Fatty acids**

Fish oil supplementation may improve psoriasis, however higher doses, and likely long treatment periods, may be necessary for the good clinical effects.[61] A review of clinical trials evaluating fish oil for the treatment of psoriasis found moderate evidence of benefit, with 12 of the total 15 trials reviewed showing clinical benefits.[62] Positive clinical trials have used an average dose of 4 g eicosapentaenoic acid (EPA) and 2.6 g docosahexaenoic acid (DHA) daily which needed to be taken for at least 6 weeks to 6 months to see improvement; typically, a range of reduction in symptom score of 40-75%.[63] In addition to fish oil supplements, advice to consume 170 g of omega-3 rich fish daily for 6-weeks was also effective.[64] Beyond reduction of psoriasis dermatological symptoms benefits have also been observed for related sequel including risk factors for obesity, cardiovascular disease, and metabolic disease as well as reductions in several inflammatory mediators.[65]

- **Vitamin A**

Synthetic retinoids are used for the management of psoriasis, but their use is limited by adverse effects, especially mucocutaneous and hepatic side effects resembling hypervitaminosis A syndrome.[66] Oral vitamin A has been explored for psoriasis, however, was abandoned early on due to inadequate clinical response and toxicity.[67] A potential alternative to vitamin A is the pro-vitamin A carotenoid β-carotene as it is non-toxic. A clinical trial tested the effect of β-carotene in adults with mild, chronic, plaque-type psoriasis (n=34) at a dose of 30-40 mg twice daily with meals for 12-weeks. Compared to placebo, β-carotene significantly reduced symptoms scores with no mucocutaneous side effects or adverse effects on liver function or lipid profiles associated with vitamin A or synthetic retinoids.[68]

- **Vitamin D**

Vitamin D deficiency has been associated with psoriasis, and while benefits of repletion on dermatological manifestations of psoriasis are equivocal, assessment and supplementation in cases of deficiency would have wide-ranging health benefits beyond the skin including on immunological function and metabolic health.[69] Findings have suggested that vitamin D deficiency is typically more severe in patients with psoriasis, and that the degree of deficiency correlated with disease duration and severity.[70] [71] [72]

Supplementation with the active form of vitamin D (1,25-dihydroxyvitamin D) was shown to result in an 88% response rate with 26.5% of patients experiencing complete remission.[73] Very high dose vitamin D3 (35,000 IU once daily for six months) and a low-calcium diet significantly improved symptom scores in patients with psoriasis.[74] And a case report described resolution of adalimumab-induced psoriasis in a woman with rheumatoid arthritis after treatment of vitamin D deficiency with vitamin D3.[75] In contrast, a meta-analysis of four clinical trials found that vitamin D supplementation did not significantly improve symptoms scores suggesting that it is currently uncertain if low 25(OH)D levels represent a contributory cause or consequence of psoriasis.[76] Collectively these reports suggest a high frequency of vitamin D deficiency in patients with psoriasis, but it is unclear if this would significantly impact disease activity.

- **Folate**

Caution should be used with high-dose folic acid and 5-methyl tetrahydrofolate (5MTHF) in patients with psoriasis receiving methotrexate. Administration of folic acid at a dose of 2.8 to 5 g daily has

been shown to reduce the effectiveness of methotrexate in psoriasis patients already in remission.[77] [78] And 5MTHF at a dose of 15 mg daily was reported to result in a psoriasis flare in an individual receiving methotrexate.[79] Lower doses of folic acid and 5-formyl tetrahydrofolate (folinic acid), however, have been shown to reduce methotrexate gastrointestinal side effects and hepatic dysfunction (elevated serum transaminase levels) and improve methotrexate compliance in patients with rheumatoid arthritis.[80] For psoriasis patients receiving <15mg methotrexate weekly a dosage regime of 5 mg of folic acid per day for 2 days after the last dose of methotrexate has been proposed, with an additional third dose of 5 mg on day 3 for patients receiving > 15 mg.[81]

A higher prevalence of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism has been found in patients with psoriasis, suggesting a possible association with disease development and severity.[82] [83] However, few studies have explored folate or other nutrients involved in one-carbon metabolism as a stand-alone therapy for psoriasis. A small study of folic acid at a dose of 5 mg twice daily and B12 injections found no effect on symptoms.[84]

- **Vitamin B12**

It is possible that vitamin B12 deficiency may contribute to psoriasis disease activity and that improving nutritional status reduces symptoms, but evidence from research is mixed. Nonetheless, a higher prevalence vitamin B12 deficiency and elevated homocysteine associated with low B12 status could be associated with disease severity in some patients.[85] [86] Of two clinical studies examining the effects of intramuscular vitamin B12, one reported good improvement in clinical symptoms while another found no benefit.[87] Taken together it would be prudent to screen patients with psoriasis for vitamin B12 deficiency.

- **Chromium**

Psoriasis has been associated with a higher prevalence of insulin resistance, type 2 diabetes risk and metabolic syndrome.[88] [89] Although insulin resistance is often considered a co-morbidity there is evidence to suggest that poor insulin metabolism could adversely affect skin physiology by contributing to the pro-inflammatory state in psoriasis.[90] Some evidence supports a causal role, including correlations between insulin resistance and disease severity,[91] and exacerbation of psoriasis with insulin therapy but risk-reduction with oral hypo-glycemic agents.[92] [93] Dietary supplementation with the insulin-sensitizing mineral chromium at a dose of 600 µg daily for 6-weeks improved both insulin resistance and psoriasis severity, but only in patients with established insulin resistance.[94] Nutritional and lifestyle-based management of insulin-resistance is an important consideration.

- **Antioxidant nutrients**

Systemic oxidative stress (overproduction and/ or inadequate removal of reactive oxygen species) is a consistent feature of psoriasis that plays a role in disease development and is an important target for patient management.[95] Oxidative stress could contribute to the development of psoriasis through a number of mechanisms, including DNA modification, lipid peroxidation, and production of inflammatory cytokines.[96] The oxidative stress characteristic of psoriasis is broadly due to exposure to pro-oxidant stimuli and impaired endogenous antioxidant defenses.[97]

Nutritional interventions that target oxidative stress, sequestering oxidants and improving endogenous defenses, can be useful clinically.[98] A clinical study of coenzyme Q10 (50 mg daily), vitamin E (natural alpha-tocopherol, 50 mg), and selenium (aspartate salt, 48 µg) resulted in

improvements several parameters related to oxidative stress, included superoxide production, copper/zinc-superoxide dismutase, and catalase, as well as a significant reduction in disease severity which correlated with normalization of the oxidative stress markers.[99] In contrast, selenium with or without vitamin E has failed to reduce clinical symptoms, despite some improvement in metabolic markers.[100 101 102]

Vitamin C (ascorbic acid) has been found to complement NB-UVB phototherapy. In 12-week clinical trial patients with psoriasis (n=74) were assigned randomly to NB-UVB only or NB-UVB with vitamin C (500 mg twice daily). Compared to NB-UVB only the addition of vitamin C significantly improved redox balance (increasing serum vitamin C and glutathione while decreasing malondialdehyde) which correlated significantly with symptomatic improvement.[103]

Addition of ubiquinone (CoQ10) to a biological medicine (adalimumab) to adult patients with psoriasis over 3-months resulted in a significant reduction in symptoms scores and improvement in quality of life when compared to adalimumab plus placebo.[104] CoQ10 was chosen as a therapeutic due to its antioxidant action and the role of oxidative stress in psoriasis.

- **Turmeric**

Turmeric (Curcuma longa) has a long-history of use for a wide variety of dermatologic disease, which may be in part due to its anti-inflammatory, antimicrobial, and antioxidant properties.[105] Extracts of turmeric have shown promise as an adjuvant to standard therapy. The addition of 600 mg turmeric extract providing 72 mg of curcumin daily resulted in a good therapeutic response to phototherapy with ultraviolet (UV)-A radiation or visible blue light applied locally,[106] and was more effective than conventional treatment with methoxsalen and psoralen plus UV-A therapy.[107]

Clinical trials suggest that a specific enhanced -bioavailability turmeric extract may be more effective. An initial clinical trial with turmeric extract providing 4,500 mg per day of curcuminoids for 12-weeks found no benefit.[108] However, a second trial utilizing an enhanced bioavailability formulation (Meriva; Indeena, Italy) providing 400 mg curcumin daily reduced symptoms more effectively than topical steroids alone.[109]

- **Bile acids**

Bile acids have been reported to be a successful management approach for psoriasis with the primary mechanism suggested to be due to their ability to degrade gastrointestinal-derived endotoxin and prevent its systemic migration and direct adverse effects on the skin.[110] Primary biliary cirrhosis and its associated cholestasis may have a causal role in psoriasis.[111] Bile acids have also been shown to directly improve psoriasiform dermatitis by inhibiting Th17 differentiation and production of the cytokine IL-17A.[112]

In a trial (n=800) of oral bile acids (dehydrocholic acid 250 mg 2-3 times daily for 1–6 and 3–8 weeks in acute and chronic cases, respectively) and conventional therapy (topical treatments, antibiotics and antihistamines) vs. conventional therapy alone it was found that 78.8% or patients became asymptomatic vs. only 24.9% of those receiving conventional therapy. Bile acids were found to be more effective during the acute phase of the disease with 95.1% of patients becoming asymptomatic.[113] At 2-years follow up 57.9% of those who received bile acids remained asymptomatic, compared to 6.0% receiving the conventional treatment with more pronounced benefit in acute phase patients (79.9% asymptomatic vs. 7.2%). A series of case reports describe resolution of psoriasis after treatment of fatty liver disease with bile acids (ursodeoxycholic acid 300 mg to 600 mg daily).[114] A number of other investigators have described similar success in managing

psoriasis with ursodeoxycholic acid.[115] [116] And a dermatologist has reported his own clinical successes with using bile acids for numerous patients with psoriasis.[117] Over-the-counter products utilized include Jarrow Formulas; Bile acid factors providing 1000 mg total bile acids per capsule and Allergy Research Group; Ox bile providing 125 mg or 500 mg per capsule. Concomitant use of dietary therapies (low fat, mostly vegetables, avoid alcohol, peppers and emulsifiers) as well as bioflavonoids (quercetin), turmeric extract and silymarin are recommended as components of an integrative approach. [118]

- **Topical therapies**

Herbal and nutritional topical therapies that have been examined in clinical trials, including Aloe vera, avocado oil, Curcuma longa, capsicum frutescens, Hypericum perforatum, and Mahonia aquifolium, and have generally resulted in good clinical benefits when applied 2-3 times daily for 4-16 weeks with a high degree of safety.[119]

Aloe vera cream (0.5% in hydrophilic cream) cured 25/30 (83.3%) adults with slight to moderate psoriasis compared to a placebo cure rate of 2/30 (6.6%) in one study.[120] And in another Aloe vera gel (70% aloe mucilage) was more effective than triamcinolone acetonide for relief of the clinical symptoms of psoriasis.[121]

A vitamin B12 cream containing avocado oil was well-tolerated and effective for reducing symptom score in chronic plaque psoriasis.[122] Similarly, a vitamin B_{12}-containing ointment had significant clinical superiority when compared to a glycerol-petrolatum-based emollient cream for the treatment of mild-to-moderate plaque psoriasis.[123]

Summary and Clinical Considerations

Intervention	Discussion	Guidance
Healthy diet	Unhealthful dietary practices appear to be more frequent in patients with psoriasis and could increase disease risk and severity. Conversely, healthy dietary interventions improve the disease course.	Increasing vegetable intake, low consumption of meat, avoidance of junk food and sugar, and specific foods, such as black coffee, black tea, chocolate, pepper, smoked foods, monosodium glutamate, and alcoholic drinks may be useful. Consider dietary supplements to optimize nutritional intake and support skin health.
Weight-loss diet	Overweight and obesity can contribute to disease severity though increased low-grade inflammation and diet-induced weight loss results in clinical improvement.	Dietary and lifestyle-based weight loss regimes, including low-energy diets and very low carbohydrate ketogenic diets, can be considered a component of nutritional management for overweight or obese patients.
Gluten-free diet	There is a higher frequency of celiac disease and gluten sensitivity in psoriasis, and gluten-free diets may reduce disease severity.	Confirmed celiac disease must be managed with a strict gluten-free diet, however, a gluten-free diet should be considered even in the absence of histologically confirmed celiac disease or positive antibodies i.e., non-celiac gluten sensitivity.

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Intestinal permeability-targeted diet	Nutritional modification of intestinal permeability could benefit psoriasis, but although research is limited.	Assessment of intestinal permeability and, if indicated, a permeability-targeted nutritional intervention might be considered.
Fatty acids	Both high-dose fish oil and increasing fish consumption can be effective for reducing symptoms.	Consider around 4 g EPA and/ or 2.6 g DHA or advice to consume 170 g of omega-3 rich fish daily for >6-weeks.
Vitamin A	The pro vitamin A carotenoid β-carotene has been shown to reduce psoriasis symptoms without the side-effects of vitamin A or synthetic retinoids.	Consider β-carotene 30-40 mg twice daily with meals for >12-weeks.
Vitamin D	Vitamin D deficiency may be more severe in psoriasis, and the degree of deficiency has been correlated with disease duration and severity.	Vitamin D supplementation with vitamin D3 could be considered in the presence of vitamin D deficiency.
Folate	High-dosed folic acid and 5-methyl tetrahydrofolate (5MTHF) methotrexate as it may reduce methotrexate efficacy, while lower doses may reduce side-effects.	For patients receiving <15mg methotrexate weekly consider a dosage regime of 5 mg of folic acid per day for 2 days after the last dose of methotrexate, with an additional third dose of 5 mg on day 3 for patients receiving > 15 mg.
Vitamin B12	Vitamin B12 deficiency may exacerbate disease activity and improving nutritional status could reduce symptoms, but evidence is mixed.	It would be prudent to screen for vitamin B12 deficiency.
Chromium	Poor blood glucose metabolism could contribute to psoriasis in a subset of people and may be positively impacted by chromium.	Consider chromium supplementation 600 µg daily for 6-weeks in patients with established insulin resistance.
Antioxidant nutrients	Systemic oxidative stress is a consistent feature of psoriasis and may contribute to disease development and be an important target for management.	Consider trialing a nutritional antioxidants, especially multi-nutrients formulations, CoQ10, and vitamin C.

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Turmeric	Turmeric extracts have shown promise as an adjuvant to standard therapy.	Consider an enhanced-bioavailability extract providing 400 mg curcumin daily.
Bile acids	Bile acids may degrade gastrointestinal-derived endotoxin and prevent its systemic migration and direct adverse effects on the skin.	Consider bovine bile concentrate 500 mg 1-3 times daily with meals.[124]
Topical therapies	Several herbal and nutritional topical therapies that have been examined in clinical trials with good results.	Aloe vera cream or gel is widely available and has generally resulted in good clinical benefits when applied 2-3 times daily for 4-16 weeks.

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