REVIEW

Lupus Erythematosus and Nutrition: A Review of the Literature

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The purpose of this review was to search the scientific literature for dietary compounds that alleviate or exacerbate symptoms of lupus erythematosus (LE) in both animal and human models. A detailed literature review was undertaken to find articles showing a relationship between LE and nutrition by using MEDLINE/INDEX MEDICUS (1950-March 2000) for English-language articles, followed by cross-referencing. Aggravating substances appear to include excess calories, excess protein, high fat (especially saturated and omega-6 polyunsaturated fatty acids), zinc, iron, and L-canavanine found in alfalfa tablets. Possible beneficial dietary compounds include vitamin E, vitamin A (beta-carotene), selenium, fish oils (omega-3 polyunsaturated fatty acids), evening primrose oil, flaxseed, a plant herb (*Tripterygium wilfordii*), dehydroepiandrosterone, and calcium plus vitamin D (if taking corticosteroids). Some people with systemic LE placed on food allergy elimination diets reported improvement in their LE symptoms; however, this may be related to a decrease of other substances in the diet. Also, although no direct evidence was reported on the beneficial effects of either bromelain or a vegetarian diet (possibly allowing fish), it is suggested that they might be beneficial. Limitations to this research are that the findings are based on relatively few studies, many of which were without control groups or extrapolated from animal models. No large-scale studies have been performed with LE patients to substantiate the benefit, if any, of these individual dietary interventions, and if they were conducted, the remission and exacerbation pattern of LE may interfere with elucidating their effectiveness. Also, dietary changes should not be attempted without a physician's approval/monitoring.

THE RELATIONSHIP between nutrition and lupus erythematosus (LE) remains elusive,[1] especially because most autoimmune diseases are multifactorial in origin with genetic, environmental, hormonal, viral, and psychoneurological influences all playing a role.[1,2] It is known that no specific diet for the treatment of LE exists; however, a review of the literature investigating the influence of nutrition in both animals and humans suggests that certain substances in the diet may aggravate or alleviate LE symptoms (Tables 1 and 2).

This article elaborates on many of the studies behind the various dietary compounds listed in Tables 1 and 2 that may aggravate or alleviate LE symptoms. Although much of the research presented in this review article is based on animal studies, those involving human experiments are also discussed. Human subjects are designated as having discoid or systemic lupus erythematosus when specified in the literature, or ''LE'' if no such designation was provided.

Possible Harmful Substances

Excess Energy

Most animal studies suggest that energy restriction ameliorates autoimmune disease[3,4] and increases longevity in New Zealand black or white mice, which spontaneously develop an autoimmune disease resembling systemic LE.[5-8] The disease in these mice is manifested by synthesized antibodies to double-stranded DNA, high levels of circulating immune complexes (a marker of systemic lupus erythematosus [SLE] clinical activity), and deposition of the latter in the renal

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Table 1. Possible Harmful Dietary Substances Related to Lupus Erythematosus

Possible Harmful Substances	Suggested Maximum Daily Intakes*
Excess energy	2400-2600 calories (men)/ 1600 calories (women)†
Excess protein	63 g (men)/50 g (women)
High fat (especially saturated and polyunsaturated omega-6 fatty acids)	30% of calories/65 g (total fat) 10% of kilocalories/20 g (saturated fat)
Zinc	15 mg (men)/12 mg (women)
Iron	10 mg (men)/15 mg (women)
L-canavanine (alfalfa tablets)	NA

Abbreviation: NA, not applicable.

*Based on the 1989 Recommended Dietary Allowances (RDA) for adults 25 to 50 years, 1997 Dietary Reference Intakes (DRI), Reference Daily Intakes (RDI), and Daily Reference Values (DRV).

†These values represent the average daily caloric intake of Americans (the majority of which are overweight) and are below the RDA values for men (2900 kcal) and women (2200 kcal).

glomerulus. As a result, glomerulonephritis is the major cause of death with mortality rates averaging 50 percent by about 8.5 months.[9]

Caloric restriction delays the onset of glomerulonephritis in these mice; however, this dietary manipulation is severe and initiated early—parameters that cannot be duplicated in the human model because caloric restrictions would be equivalent to 25 to 35 percent or more of total intake before adolescence. The degree of energy restriction in one mice study was even higher at 60 percent (at 2 months of age) versus the control group allowed to feed ad libitum. At 14 months, the percentage of these mice still living that had not died as a result of renal disease was 100% and 0%, respectively.[10] Although there are no studies showing the effect of caloric restriction in humans, Kipen et al[11] reported that SLE disease activity was associated with an increase in body mass index over a 3-year period in premenopausal women (n = 55).

In terms of animal models, the exact mechanisms by which energy restriction benefits autoimmune conditions are still being explored. Safai-Kutti et al[12] reported a reduction in circulating immune complexes, occurring in mice eating an energy-restricted diet, while Chandrasekar et al[13] observed a decrease in proinflammatory cytokines. Mizutani et al[14] reported that reducing calories to 32 percent or less than controls in autoimmune-prone mice resulted in decreased immunoprecipitates, less coronary vascular lesions, and fewer glomerular lesions. Restricting calories in mice was reported by Meydani et al[15] to also reduce prostaglandin E_2 (PGE_2) synthesis, another compound known for its proinflammatory effects. One study restricting calories in mice and comparing them with a control group reported a delay or inhibition of Sjogren's syndrome abnormalities, increased immunosuppressive transforming growth hormone beta-1, and decreased cytokines.[12]

Table 2. Possible Beneficial Dietary Substances Related to Lupus Erythematosus

Possible Beneficial Substances	Daily Intakes*
Vitamin E†	30 IU/9 mg alpha-TE (400-1500 IU/130-500 mg)
Vitamin A (beta-carotene)	5000 IU/1000 µg RE
Selenium	70 µg
Fish oils‡ (omega-3 fatty acids)	(1.5-3 g of EPA/DHA)
Evening primrose oil	(5 g)
Flaxseed	(30 g)
Plant herb§ (*Tripterygium wilfordii*)	(10 mg—side effects?)
DHEA‖ (dehydroepiandrosterone)	(200 mg—side effects?)
Food allergy elimination diets	NA
Calcium (if taking corticosteroids)	1000 mg
Plus vitamin D	400 IU/10 µg

Abbreviations: alpha-TE, alpha-tocopherol equivalents; RE, retinol equivalents; NA, not applicable.

*Based on the RDI. Amounts in ( ) represent tentative research data.

†High dosages of vitamin E act as an anticoagulant.

‡Most fish oil capsules contain about 300 mg of omega-3 fatty acids, so about 2 to 3 tablets/meal will yield 1.8 to 2.7 g.

§Previously reported side effects include, but are not limited to, gastrointestinal upset, infertility, suppression of lymphocyte proliferation, and possible cardiac toxicity and birth defects.

‖Caution: People should not take DHEA unless under the care of their physician who approves such a regimen. The benefits of DHEA reported in people with lupus occurred at high, and questionable, intakes of 200 mg/day. DHEA is an androgenic with male hormonal influences, and dosages as low as 50 mg/day have been reported to cause minor side effects such as acne, facial hair growth, menstrual changes, and improved mood. There are also animal studies in which DHEA appears to cause liver cancer in rats.

Excess Protein

Low-protein diets are also known to improve survival rates in autoimmune mice.[6] Mice fed a moderately restricted protein diet experienced longer lasting immunologic functions and delayed development of autoimmunity when compared with mice fed a normal protein diet.[16]

These results are not surprising because high protein intakes have been commonly associated with acceleration of kidney damage in both autoimmune-prone humans and experimental animals.[17] Protein restriction has long been the standard treatment for renal failure.[18]

After establishing that the amount of dietary protein influenced the outcome of autoimmune-prone mice, researchers focused on specific types of protein. One study indicated that limiting proteins containing high levels of phenylalanine and tyrosine, such as those found in beef and dairy products, is beneficial to mice with a systemic LE–type condition.[4] Carr and others[19] reported that 12 of 15 mice fed a casein-free diet were still alive at 10 months, compared with only 1 in 10 mice on the control diet, and that casein-free mice had less anti-DNA antibody and immunoreactants in the glomeruli. Another amino acid in question is tryptophan because elevated urinary excretion levels of tryptophan metabolites were reported in 11 discoid lupus patients.[20] Researchers have also suggested that tryptophan breakdown products may lead to autoantibody production,[21] and a research study investigating this possibility determined that a tryptophan-deficient diet fed to lupus animals resulted in longer survival times.[22]

The average American ingests about 100 g of protein a day, an amount that can be reduced by almost half in healthy people without jeopardizing their protein requirements. The Recommended Daily Allowances (RDA-1989) for protein are 50 g for women and 63 g for men in the 25 to 50 years age group. Vegetarian diets often automatically reduce dietary protein, and there was a case study reported of a patient with SLE who went on a vegetarian diet (0% animal protein). Her antibody titers returned to normal, urinary protein excretion decreased, and serum albumin rose. Although protein dropped from 97 to 32 g, so did calories (2295 to 1216) and grams of fat (70 to 50).[23] The caloric reduction, along with the fact that this is a single-case study and that the possibility of remission exists, does not warrant any dietary recommendation; however, further study in this area is suggested.

High Fat (Especially Saturated Fat and Omega-6 Polyunsaturated Fatty Acids)

Diets high in overall fat were associated with more severe autoimmune disease and decreased life span in mice compared with a control group, whereas low fat diets were reported to retard the development of disease.[24,25]

The type of dietary fat also dramatically affects the onset of autoimmune disease in mice, particularly if it consists of saturated or omega-6 polyunsaturated fatty acids. Alexander et al[26] reported that by 10 months of age, the percentage of mice still alive was: 94% of the fish oil (omega-3 polyunsaturated fatty acids) group, 35% of the mice fed corn oil (omega-6 polyunsaturated fatty acids), and 0% of the group fed saturated fat in the form of lard (n-9 fatty acids). Fernandes et al[27] supported these results with a study showing that omega-3 fatty acids lowered the severity of autoimmune disease in mice, whereas both saturated (n-9) and polyunsaturated (n-6) dietary lipids exacerbated the disease.

Autoimmune-prone mice fed saturated fats experience more severe nephritis and glomerular pathology.[28,29] Several researchers have reported that mice fed saturated fat diets produced higher levels of autoantibodies than those on low fat or high unsaturated fat diets.[28,30,31] High fat diets in mice have also been reported to increase proteinuria,[24,32] PGE_2 production, cytokine levels (interleukin-6),[33] and macrophage function.[24] These types of results have led some researchers to suggest that dietary fat, especially saturated fat, restriction may be an effective therapeutic approach to murine lupus nephritis.[29]

Several studies suggest that limiting essential omega-6 fatty acids and/or zinc may suppress immune response, and therefore flare-ups. Hurd and Gilliam[34] postulated that some of the prostaglandins or related products of arachidonic acid (prostacyclin, thromboxane, or lipoxgenase pathway products) may be necessary for the full expression of autoimmunity. Essential fatty acid deficiency in mice resulted in an increased survival time, delay in antibody production, and less severe renal disease.[35,36] However, researchers of another study reported that the survival of mice

(MRL/I) was not affected by polyunsaturated fatty acid deficiency.[37] In studies that do show positive results, limiting essential fatty acids may be beneficial because less are then available for the synthesis of specific prostaglandins responsible for inflammation.

Thorner et al[38] conducted one of the few human studies in which SLE patients reduced their omega-6 polyunsaturated fatty acid intake. After 1 year, the number of patients with active SLE dropped from 11 to 3. Spontaneous improvement, placebo effects, and lack of a control group must be considered as possible influences in this and other studies investigating the role of diet on LE symptoms. However, the researchers suggested the possibility of reducing the intake of omega-6 polyunsaturated fatty acids as a nonpharmacological approach to the treatment of patients with SLE. Foods high in omega-6 fatty acids are listed in Table 3.

Zinc

Zinc is important for enhancing the immune response, and MRL/1 mice on zinc-deficient diets were reported to have increased survival times. Researchers observed a decrease in lymphoproliferation[39] and a delayed expression of autoantibodies.[40] It has been suggested that zinc deprivation results in increased serum corticosteroids, which may contribute to the decreased number of autoimmune disease symptoms.[39]

Iron

Only one animal study suggests that high iron intakes, 7 times the requirement, in mice resulted in high proteinuria, renal histopathology, and mortality. The researchers theorized that excess iron may enhance the Haber-Weiss reaction, causing free radical damage of the tissues. During an inflammatory response, neutrophils and macrophages release superoxide (O_2) and hydrogen peroxide (H_2O_2), and the reaction of these compounds with iron produces a highly toxic hydroxyl radical (OH).[41] A source of high iron for humans is ingestion of prenatal vitamin/mineral supplements that often contain 30 to 60 mg (Recommended Dietary Allowance [RDA] for women = 15 mg/d).

Alfalfa (L-Canavanine)

Researchers studying the cholesterol-lowering effect of alfalfa seeds observed signs of SLE-like symptoms in both laboratory animals and a few human case studies.[42-44] Two human patients were reported to experience symptoms of malaise, lethargy, depression, and arthralgias after ingesting 8 to 15 alfalfa tablets daily.[45] In vitro experiments suggest that L-canavanine, an amino acid in alfalfa products, acts on suppressor-inducer T cells to regulate antibody synthesis and lymphocyte proliferation.[46] Feeding L-canavanine to autoimmune mice resulted in increased antibody production and higher renal histology scores.[47] However, a company reported their alfalfa tablets tested negative for canavanine (with a detection limit of 5 ppm), and that alanine, an amino acid, has previously been mistaken for canavanine.[48]

Possible Beneficial Substances

Vitamin E

Although animal studies on MRL/lpr mice show that vitamin E treatment delays the onset of autoimmunity and extends mean survival time,[49] treating LE patients with vitamin E continues to be controversial. Vitamin E studies related to LE first started to appear in the late 1940s, and a historical overview of the literature reveals that large vitamin E doses may be beneficial in some cases, whereas dosages below 300 IU may not be sufficient.[50] For example, 4 discoid LE patients in one study, receiving 900 to 1600 IU of vitamin E daily, showed partial or complete clearing of rashes, whereas 2 patients receiving only 300 IU daily had no benefit.[51] Other human studies reporting either positive[5,52-57] or negative[58-61] results of vitamin E on discoid LE lesions are listed in Table 4.

Investigators warn that ''while the effect of mixed tocopherols in LE is apparently profound, often rapid and at times almost specific, the fact remains that recurrences are not uncommon.''[62] Also, vitamin E is a fat soluble vitamin that acts as an anticoagulant at the high dosages used in these studies, much higher than the Reference Daily Intake (RDI) of 30 IU (9 mg) alpha-tocopherol equivalents (TE). Dietary sources of vitamin E are listed in Table 3.

Table 3. Selected Foods High in Certain Nutrients Related to Lupus Erythematosus

Omega-6 fatty acid food source	g/100 g
Safflower oil	74.3
Sunflower oil	66.5
Poppyseed oil	66.5
Corn oil	57.8
Wheat germ oil	54.8
Walnut oil	52.8
Cottonseed oil	50.9
Sesame oil	41.3
Mayonnaise	36.3
Rice bran oil	33.4
Liquid margarine	33.4
Peanut oil	26.1
Brazil nuts	20.8
Tahini	23.1
Pine nuts	20.7
Pumpkin kernels	20.7
Vitamin E food source	**mgα-Tocopherol/100 g**
Wheat germ oil	183
Sunflower oil	60
Sunflower seed	57
Rice bran oil	37
Almonds	27
Filberts/hazelnuts	25
Canola oil	23
Cod liver oil (fish oil)	22
Wheat germ	18
Beta-carotene food source	**RE/100 g (cooked unless noted)**
Carrot juice (canned)	2575
Carrots (raw)	2454
Sweet potato	2182
Shallots (raw)	1250
Mixed vegetables (canned)	1164
Pumpkin	1082
Spinach	819
Kale	740
Apricot halves (dried)	723
Collard greens	598
Red bell pepper (raw)	570
Selenium food source	**µg/100 g**
Pike	190
Carp	159
Herring	141
Rainbow trout	124
Wheat germ	101
Crayfish/crawdads	100
Anchovies	90
Scallops	82
Tuna (in water)	80
Sunflower seeds	78
Lobster	77
Octopus	75
Oysters	72
Chicken livers	71
Whole wheat flour	71
Rainbow trout	71
Salmon	60
Liverwurst—pork	58
Sardines	57
Pork sirloin	52
Omega-3 fatty acid food source	**g/100 g**
Oils/nuts	
Sardine oil	22.2
Cod liver oil	18.8
Walnut oil	10.4
Canola oil	8.0
Wheat germ oil	6.9
Walnuts	6.8
Soybean oil	6.8
Mayonnaise	4.7
Fish/shellfish/soybeans	
Mackerel	1.9
Sablefish	1.9
Salmon (chinook)	1.9
Whitefish	1.9
Herring	1.7
Bluefin tuna	1.5
Soy nuts/soybeans	1.5
Atlantic sardines in oil	1.5
Oysters	1.4
Rainbow trout	1.2
Swordfish	1.1
Sea bass	1.0
Scallops	1.0

Note. Most fish oil capsules contain about 300 mg of omega-3 fatty acids; 180 mg EPA, and 120 mg DHA, 3 tablets/meal yield about 2.7 g.

Abbreviations: RE, retinol equivalents.

Nutrient analysis based on Food Processor Plus (Version 6.0), ESHA Research, Salem, OR.

Vitamin A

Vitamin A–deficient LE animals were reported to experience more severe lupus-like symptoms. Researchers attributed this observation to increased hyper-gammaglobulinemia and an earlier onset of autoantibodies, both naturally occurring thymocytoxic autoantibodies and IgM antierythrocyte antibodies.[63] Three patients whose skin lesions flared with sun exposure were administered 50 mg of beta-carotene 3 times daily, and experienced a clearing of all lesions starting within 1 week of treatment.[64] Other researchers reported that very high levels of vitamin A (100,000 U daily for 2 weeks) in SLE patients resulted in an enhancement of antibody-dependent cell-mediated cytotoxicity, natural killer cell activity, and blastogenic response to mitogens.[65]

However, patients should be cautious with

Table 4. Selected Human Studies on the Positive and Negative Results of Vitamin E on LE Lesions

Positive Results		
Reference	Dosage (per Day)	Results
52	600 mg natural mixed tocopherol	24/25 improved
53	1000-2000 mg tocopherol (synthetic & natural) + Ca pantothenate (10-15 g) or Na pantothenate (5-10 g)	Complete clearing of a majority of 67 subjects
54	300-1200 IU tocopherol + topical vitamin E	4/7 showed excellent improvement
55	300-400 mg L-tocopherol	47 subjects—beneficial only in those with recent lesions
56	150-250 mg synthetic vitamin E	17/25 recovered, but 2 relapses within 6 months
57	150 mg alpha-tocopherol followed by 300 mg + intramuscular injections	1 patient with severe facial lesions showed improvement after 1 month
Negative Results		
Reference	Dosage	Results
58	600 IU mixed natural tocopherols	2/9 improved
59	600 mg tocopherol + 400 mg intramuscularly (twice weekly)	6/45 improved
60	204 mg dL, alpha-tocopherol acetate + 50 mg/dL, alpha-tocopherol acetate or 400 mg mixed tocopherols twice weekly	5/45 improved
61	1200 mg tocopherol	0/7 improved

extremely high levels of vitamin A unless they are water-soluble, because ingesting excess vitamin A from animal sources may result in one or more of the following symptoms: anemia, headache, dry skin, hair loss, nausea, lack of appetite, bone pain, stunted growth in infants/children, pseudohydrocephalus, and death. Table 3 lists vegetable sources high in vitamin A (beta-carotene). Although excess beta-carotene from plant sources does not result in the symptoms elicited from animal sources, it can produce hypercarotenemia, turning the skin slightly orange.

Selenium (Se)

Anti-inflammatory properties have been attributed to selenium, a natural antioxidant.[66] Supplementing the diets of autoimmune mice with selenium increases their survival time, and although the mechanism by which selenium exerted this effect is unclear, there is a significantly higher level of natural killer cell activity in the selenium-supplemented mice.[67] It was also observed that low levels of blood glutathione-peroxidase (GSH-Px) exist in some patients with systemic LE, and that GSH-Px activity increased slowly after administering tablets containing 0.2 mg selenium (Na_2SeO_3) and 10 mg tocopherol succinate for 6 to 8 weeks. Some researchers have suggested that physicians could check GSH-Px activity and consider selenium and vitamin E supplementation in people with LE or other conditions, such as severe psoriasis, eczema, dermatitis herpetiforms, and liver disease.[60] Again, warnings against high intakes of selenium should be given to patients because toxicity results in symptoms of diarrhea, vomiting, hair and nail loss, and lesions of the nervous system and skin. Dietary sources of selenium are listed in Table 3.

Fish Oils

Fish oils retard, but do not entirely prevent, lupus-like disorders found in autoimmune-prone mice. These mice eventually develop the illness, but at a slower rate than controls. Fish oil supplementation appears to have an anti-inflammatory effect,[68] and prolongs the life of autoimmune-prone mice.[7,69-76] The increased life span might be caused by delayed onset of renal disease, because mice introduced to a fish oil diet as weanlings had an almost total protection against renal disease. One possible mechanism related to the beneficial effect of fish oil in autoimmune-prone mice may be related to its high omega-3 fatty acid content—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Omega-3 fatty acids inhibit the production of eicosanoids (proinflammatory compounds such as

PGE_2 and leukotriene B_4 [LTB_4]), whereas fatty acids from the omega-6 series have the opposite effect.[77-80] Arachidonic acid, an omega-6 fatty acid, is metabolized into proinflammatory eicosanoids.[81-84] Omega-3 fatty acids can displace arachidonic acid in the cell membranes,[70,74] resulting in less PGE_2 formation, and compete with arachidonic acid for cyclooxygenase and lipoxygenase enzymes.[69] This competition shifts production to the noninflammatory series-3 prostaglandins and series-5 leukotrienes that have been suggested to directly suppress immunologic and/or inflammatory mediators of murine lupus.[69,70,80] Specifically, there is a reduced synthesis of endogenous dienoic cyclooxygenase metabolites and LT 4 (LT_4), while increased synthesis of trienoic prostaglandin (PG) and LT 5 (LT_5).[69] Another factor is that omega-3 fatty acids are poor substrates for cyclooxygenase, which is the rate-limiting step in the synthesis of prostaglandins, particularly PGE_2.[78]

Omega-3 fatty acids may also inhibit the inflammatory response by decreasing T-cell activity and cytokine (stimulate prostaglandin production) concentration.[85-87] Normally, inflammation activates T cells and cytokines at the site of tissue injury and in the circulation.[82] Certain types of cytokines are also involved in peroxidation, which is a common final pathway in much of the tissue damage seen in intense inflammation. Cytokines (interleukin-1 and tumor necrosis factor-alpha) generate H_2O_2 and O_2^- in mesangial cells and macrophages, and these can result in free radical damage to the tissues. Reactive oxygen intermediates, implicated in immune-complex–mediated glomerulonephritis, affect glomerular filtration rate, impair sieving, and inhibit renal function. Reactive oxygen intermediates may react with polyunsaturated fatty acids in cell membranes, resulting in derivatives that attract inflammatory cells that can further secrete inflammatory cytokines and growth factors. Peroxidation of lipid membranes also leads to altered fluidity, and may change ion transport and enzyme activities in target tissues such as renal cells.[82] To help protect vessels and organs from the damage of excess inflammation, some researchers have suggested the administration of antioxidants such as vitamin E and selenium.[81]

Table 5. Selected Human Studies on the Benefit of Fish Oils for LE Symptoms (Clinically and Serologically)

Reference	Dosage (per day)	Results
88	3.7 g EPA/DHA	8/17 treatment and 2/17 controls improved in the first 3 months. No significant difference after 6 months
89	6 or 18 g fish oil (1.8 or 5.4 g EPA/DHA)	12 subjects—no significant improvement in immune complex, anti-DNA titer, or prostacyclin (PGI_2)
90	15 g fish oil (4.4 g EPA/DHA)	21 subjects—no significant improvement in renal function or disease activity

*"Fish oil" dosages are often reported instead of the active components—EPA/DHA.

The majority of animals studies show omega-3 fatty acids alleviating the severity of autoimmune disease, but Table 5 shows only modest anti-inflammatory effects have been reported in humans with LE.[88-90] However, omega-3 fatty acids have been reported to improve blood lipid values, which is of benefit to patients with SLE who have a higher rate of premature atherosclerosis than the general population.[89,91,92] Despite the controversy over whether or not omega-3 fatty acids benefit humans with autoimmune conditions, Kinsella[93] stated that hospital nutritional support, such as enteral and parenteral formulas in addition to intravenous emulsions, may need to be modified for use in patients with inflammatory reactions such as lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. Dietary sources of omega-3 fatty acids (EPA/DHA) are listed in Table 3.

Bromelain

Although no animal or human studies have been conducted on bromelain related to LE, this complex of proteases from the pineapple plant has been known to act as an anti-inflammatory agent.[94]

Evening Primrose Oil (EPO)

EPO was reported to increase survival time in autoimmune mice,[95] and this may be a result of its gamma-linolenic acid (19%) content from which PGE_1 is formed. Several studies support the role of PGE_1 treatment alone in delaying the onset and severity of lupus in autoimmune animals.[96-98] This beneficial effect of PGE_1 might be a result of its

anti-inflammatory effects via membrane stabilization and lowering lymphocyte activity.[99] Feeding rodents at least 5 to 10 g gamma-linolenic acid/100 g total fatty acids has been shown to decrease lymphocyte proliferation and natural killer cell activity.[100] In addition, a derivative of gamma-linolenic acid has been postulated to block the transformation of arachidonic acid to leukotrienes that have proinflammatory effects.[101]

Flaxseed

Two studies, one with mice and the other with human subjects, suggest that flaxseed may be beneficial. A 15% flaxseed diet provided to mice, and compared with a control diet, resulted in decreased proteinuria, spleen lymphocyte proliferation, and mortality. Flaxseed also appeared to preserve glomerular filtration rate.[102] Eight humans with SLE were given 30 g of flaxseed mixed in with their cereal or juice (tomato or orange), and were reported to have improved renal function defined by decreased proteinuria, decreased serum creatinine, and increased creatinine clearance. Also noted in these human subjects was the ability of flaxseed to inhibit platelet activating factor (PAF)–induced platelet aggregation.[103] PAF, a participant in the inflammatory response, is often elevated in LE patients. Studies in lupus animal models suggest that inhibiting PAF resulted in decreased proteinuria and increased survival times.

Flaxseed is one of the richest food sources for lignans that are natural antagonists to PAF receptors. This plant food is also high in an omega-3 fatty acid, alpha-linolenic acid.[103] It has been reported that the beneficial affect of these and possible other compounds in flaxseed is best achieved by ingesting it in its whole form, rather than in its oil (linseed oil) or defatted form.[104] Regardless of the form ingested, patients should be cautioned of possible allergic reactions.[105]

Plant Herb

Tripterygium wilfordii hook F (TWH), also known as Thunder God Vine, is a plant that has been used in China for more than 2000 years to treat SLE and rheumatoid arthritis.[106-109] In vitro tests support this traditional practice through evidence that the plant has immunosuppressive qualities.[110] Ramgolam et al[111] reported that TWH inhibited lymphoproliferation (mitogen-stimulated), production of cytokines by monocytes and lymphocytes, and PGE_2 production via the cyclooxygenase pathway.

Despite the promising benefit of TWH, it is difficult to evaluate the use of herbal therapies because their apparent successes and sometimes serious side effects are often not documented. Reported side effects of TWH include gastrointestinal upset, infertility, and suppression of lymphocyte proliferation. At least one case was reported of a previously healthy young man who died of shock possibly related to cardiac toxicity.[112] As with most herbs, its use during pregnancy or lactation is not recommended; a report exists of a woman taking TWH during pregnancy and giving birth to a child with a protrusion in the lower back of its head (occipital meningoencephaloecele).[113]

DHEA (Dehydroepiandrosterone)

Although not a nutrient or a dietary supplement, this steroid hormone can be purchased over-the-counter. Animal studies with autoimmune-prone mice have shown that DHEA produces similar results to those obtained with caloric restriction—decreased antibody synthesis and prolonged survival rates.[114-116] In humans, a double-blind, placebo-controlled study of 28 SLE patients taking DHEA (200 mg/d) for 3 months resulted in decreased lupus flares, SLE Disease Activity Index scores, disease activity (assessed by physicians and patients), and prednisone dosages. The researchers observed only mild acne as a side effect and concluded that DHEA may be a useful therapeutic agent for the treatment of mild to moderate SLE.[117] Several other human studies, however these without control groups, also indicated that DHEA might be beneficial to patients with LE.[118-121]

Immune responses are often influenced by sex hormones.[122] Androgens naturally suppress the immune system and concomitant inflammation, whereas estrogens can do either, although they usually accelerate autoimmunity.[123] DHEA is an androgen and an intermediate compound in testosterone synthesis. Women with autoimmune diseases like LE and rheumatoid arthritis have lower plasma androgens than controls, and researchers theorize that the ingestion of weak androgens, like DHEA, may improve the clinical manifestations of the disease.[124,125]

The androgenic nature of DHEA in women taking over 50 mg a day suggests that a doctor's supervision and caution should be elicited. Minor side effects at this dosage in women include acne, facial hair growth, menstrual changes, and improved mood; however, these symptoms disappeared after DHEA intake was stopped. Short-term studies usually report no serious side effects in humans ingesting DHEA,[126] but long-term trials have not been performed and androgen replacement remains in the realm of clinical investigation.[127] There is the possibility that DHEA can convert into certain sex hormones,[128] and there is speculation about its safety because it has been linked to hepatic cancer in rats.[129]

Food Elimination Diets

Some researchers have reported that LE patients may be more prone to food allergies.[130,131] Several case studies indicate that systemic LE patients experience remissions after food elimination diets.[132,133]

Calcium Plus Vitamin D (if Taking Corticosteroids)

Calcium and vitamin D are not reported to alleviate symptoms of LE; however, they are recommended as part of the treatment against osteoporosis, the most serious side effect of long-term corticosteroid therapy.[134] The long-term use of corticosteroids, the most commonly prescribed immunosuppressants,[135] are responsible for an estimated 20 percent of the 20 million osteoporosis cases in the United States. One in four of these patients experiences a fracture,[136] but unlike other forms of osteoporosis, the majority of corticosteroid-induced osteoporosis fractures are at the spine.[134] This is a particular concern for SLE patients that have been reported to have reduced bone mineral densities compared with matched healthy controls.[137,138]

Cushing[139] first associated skeletal mass loss with hypercortisolism in 1932; however, patients prescribed long-term corticosteroid therapy are not always (1) informed of the osteoporosis risk, or (2) provided any form of osteoporosis prophylaxis. Researchers in one study reported that only 5.6 percent of 214 patients in a British hospital receiving corticosteroid therapy (37 percent for 4 or more months) were administered treatment to help delay the onset of osteoporosis.[140]

To combat the long-term negative side effects of corticosteroids, the American College of Rheumatology (ACR) has formulated optimal medical management guidelines to reduce the risk of bone loss in patients. Preventative treatment should begin as soon as long-term corticosteroid therapy is started and include baseline bone mineral test, lowest effective dosage, hormone replacement therapy, medication, reducing risks for falls, lifestyle (weight-bearing exercise, and avoiding smoking, immobilization, and amenorrhea), and nutrient supplementation (supplements for calcium [up to 1500 mg] and vitamin D [20 µg {800 IU}, less in children]).[136] Another approach would be to initially seek these nutrients through food sources and not to exceed supplementation in excess of 10 µg (400 IU) for vitamin D. Other nutrient factors to reduce include eliminating excess protein, salt, alcohol, or caffeine. Side effects of excess calcium supplements include constipation, headaches, calcification of the soft tissues, and certain kidney stones. Vitamin D supplements should also not be taken in excess, because they have been reported to cause headache, nausea, calcification of the soft tissues and bone, a tendency toward kidney stones, and in children—possible stunted growth, mental retardation, and death by renal failure.

Conclusion

No dietary recommendations currently exist for LE patients; however, physician researchers postulated over 15 years ago that diet might be one of the possible future therapies for people with LE.[141] Tables 1 and 2 provide tentative dietary suggestions based on a literature review. Patients with LE may benefit from a balanced diet limited in calories and fat (especially saturated and omega-6 polyunsaturated fatty acids), containing rich sources of vitamin E, vitamin A (beta-carotene), selenium, and calcium. Supplements of fish oil, EPO, flaxseed, a plant herb (*Tripterygium wilfordii*), DHEA (under a physician's care), and calcium plus vitamin D (if taking corticosteroids) may also be beneficial. Foods high in omega-3 polyunsaturated fatty acids are recommended and include fish oils, fatty fish, certain vegetable oils such as walnut and canola, and soybeans. Conversely, foods to be avoided that contain omega-6 polyunsaturated fatty acids are vegetable oils made from corn, cottonseed, poppyseed, safflower,

sesame, soybean, sunflower, and walnut. People with LE may also benefit by avoiding supplements containing protein, omega-6 polyunsaturated fatty acids, zinc, and iron. Avoiding an excess of foods rich in these compounds might possibly be beneficial and would consist of limiting meats (protein), dairy (protein), oysters (zinc), Brazil nuts (zinc), and enriched grains and cereals, including breakfast cereals (zinc and iron). It may also be judicious to avoid alfalfa tablets or alfalfa in any form including sprouts. Remissions have been reported in people with LE going on food elimination diets, and perhaps these could be tried by LE patients in an attempt to alleviate flare-ups or eliminate the possibility of any existing food allergies. Further investigation should be conducted on the possible beneficial use of bromelain and vegetarian diets in people with LE.

Again, these tentative dietary suggestions are based on a literature review, and the nature of remissions occurring in people with LE along with any medications make it difficult to evaluate their effectiveness. The purpose of this article was to elucidate from the scientific literature the dietary compounds that alleviate or exacerbate symptoms of LE in both animal and human models. Extrapolations are tenuous at best, and the lack of control groups and/or use of animal studies sheds questionable query on the results. However, an ample array of research has been conducted, and the results are summarized in the form of Tables 1 and 2. This compilation is based on a limited number of studies, and no large scale studies have been performed with LE patients to substantiate the benefit, if any, of these dietary interventions. However, the possibility exists that patients with LE may benefit by incorporating one or more of these dietary modifications with the approval/monitoring of a physician.[142]

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