Diet and nutritional aspects in systemic lupus erythematosus

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ABSTRACT

The authors reviewed the influence of nutritional factors on systemic lupus erythematosus (SLE) and discussed an alternative treatment option. The autoimmunity and inflammatory process of SLE are related to the presence of dyslipidemia, obesity, systemic arterial hypertension, and metabolic syndrome, which should be properly considered to decrease cardiovascular risk. A diet with moderate protein and energy content, but rich in vitamins, minerals (especially antioxidants), and mono/polyunsaturated fatty acids can promote a beneficial protective effect against tissue damage and suppression of inflammatory activity, in addition to helping the treatment of those comorbidities. Diet therapy is a promising approach and some recommendations may offer a better quality of life to patients with SLE.

Keywords: systemic lupus erythematosus, diet, nutrition assessment, nutrition programs.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic chronic inflammatory disease of unknown cause and autoimmune nature, characterized by the presence of several autoantibodies.[1] In addition to the specific aspects related to its medicamentous treatment, some supportive measures, such as instructions about the disease, psychosocial support, physical activity, and especially the dietary approach, are essential to provide comprehensive health care to patients with SLE.[1] In fact, diet can help to control the inflammatory findings of the disease and the complications derived from its own therapy. Considering that the cardiovascular risk seems increased in patients with SLE due to the increased frequency of conditions associated with atherosclerosis, such as dyslipidemia, diabetes mellitus (DM), metabolic syndrome (MS), and obesity, dietary guidance is important to minimize those complications of the disease.[2]

The autoimmunity and the inflammatory process of SLE are directly related to changes in the lipid profile and to the metabolism of lipoproteins in SLE. The dyslipoproteinemia of the disease is characterized by higher levels of triglycerides (TG) and very-low-density lipoprotein cholesterol (VLDL-C) associated with lower levels of high-density lipoprotein cholesterol (HDL-C).[3] Patients with both active and inactive disease show those lipid changes, which are aggravated by the higher inflammatory activity of the disease, demonstrating that SLE by itself promotes a proatherogenic lipoprotein profile.[3] A reduction in the enzymatic activity of lipoprotein lipase is responsible for determining a dyslipoproteinemia characteristic of the disease, because it reduces the catabolism of TG-rich lipoproteins (chylomicrons and VLDL-C)[4] due to either the presence of anti-lipoprotein lipase antibodies (anti-LPL)[5] or the action of the tumor necrosis factor-α (TNF-α).[6]

Several drugs used to treat SLE determine deleterious changes in the lipid profile previously altered by the disease itself, the effect of corticosteroids being of particular importance.[2,7] Their chronic use in SLE is associated with an increase in total cholesterol and its fractions and TG,[2,7] which can be

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observed after 1–2 months of treatment.[2] It is already known that, for each 10-mg/day increase in the dose of prednisone, a 7.5-mg% elevation in total cholesterol is observed.[7] In addition, corticosteroids induce the appearance of other risk factors, such as obesity, systemic arterial hypertension (SAH), hyperinsulinemia, and insulin resistance.[2,8]

Hyperinsulinemia increases oxidative stress, which is considered an important pathophysiological mechanism for the development of atherosclerosis. Some studies have evidenced that DM is significantly more common in patients with SLE than in the general population, because of the reduced insulin sensitivity, and that approximately 18%–38% of the patients have MS.[2,9,10]

It is worth noting that more than half of the patients with SLE have three or more risk factors for cardiovascular disease, particularly obesity, SAH, and dyslipidemias, suggesting that they are really more susceptible to the MS.[2,11] A Brazilian assessment of the nutritional status of 170 patients with SLE has reported a 1.2% prevalence of grade I thinness and a 64.2% prevalence of excessive weight (35.9% of overweight; 21.8% of grade I obesity; 4.1% of grade II obesity; 2.4% of grade III obesity). Eutrophy, according to the Body Mass Index (BMI), has been observed in only 34.7% of the patients assessed, leading to the conclusion that excessive weight is a frequent finding during the follow-up of patients with SLE.[12] Thus, it is extremely important to establish strategies, such as programs to encourage the practice of physical activity and body weight reduction, in addition to nutritional counseling, to reduce the risks of MS.

In addition, the hyperlipid diet (rich in cholesterol and saturated fat) is one of the major factors for maintaining dyslipidemia in SLE, perpetuating and aggravating lipid profile changes.[8,13,14] On the other hand, antioxidant nutrients, such as β-carotene, α-tocopherol, ascorbic acid, and selenium are known to protect against tissue damages by both activating macrophages, monocytes and granulocytes, and suppressing the activity of cytokines and TNF-α.[15]

Diet therapy is a promising way to approach SLE, with the indication of vitamin- and mineral-rich foods (mainly the antioxidant ones) and mono/polyunsaturated fatty acids, and moderate energy consumption, aiming at reducing inflammatory markers and helping in the treatment of those comorbidities and of the adverse reactions to drugs.[11,13,16,17]

DIET THERAPEUTIC INTERVENTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

The dietary status refers to the intake of nutrients from food and from supplements, being part of the nutritional status. The nutritional status is extremely important to the immune system balance, the diet composition assuming a fundamental role in maintaining the health of all individuals, including those with SLE.

In fact, thinness or low weight can indicate chronic energy deficiency, being, thus, associated with greater morbidity and mortality.[12,18] Overweight and obesity can also be harmful to health, depending on their duration and severity, because these factors reduce resistance, favoring infections.[12,18] Because of their deleterious effects on the immune function, both disorders should be diagnosed, aiming at improving the quality of life.

In addition, there is evidence that dietary factors can contribute to the geoepidemiology of autoimmune diseases.[19] An adequate diet can, thus, be an essential factor to improve the prognosis of immune diseases, in addition to helping to prevent infections and the progression of cardiovascular diseases.

Calories

The restriction of calories in the diet alters the progression of autoimmune diseases.[20] Some studies have shown that energy restriction around 30%–40% of the food intake prolongs the life of MRL/lpr mice by inhibiting the development of the lymphoproliferative syndrome, with a reduction in the secretion of IgG 2A (the major antibody of the autoimmune nephritis due to renal deposits) and of the platelet-derived growth factor (PDGF), which can reduce the glomerular lesion of NZB/NZW mice.[17,21–23]

Energy restriction inhibits the decrease of $CD4^+$ and $CD8^+$ T lymphocytes, in addition to attenuating the increase in Th1 cytokines (IL-2 and interferon-γ [IFN-γ]) produced in NZB/NZW mice.[22]

The National Academy of Sciences recommends the intake of 1,800–2,000 calories/day for a sedentary eutrophic adult, and of 2,200–2,500 calories/day in the presence of minimum physical activity.[24] Regarding the treatment of excessive weight, the assessment of 86 studies performed by the US National Institutes of Health[25] has shown that a diet of 1,000–1,200 kcal/day results in the loss of 7–13 kg (mean of 8%) in 3–6 months, with a mean 10-cm reduction in abdominal fat in 6–24 weeks.[25] That recommendation is also strongly supported by the British Nutrition Foundation.[26] The National Cholesterol Education Program shares the same opinion, recommending a deficit of 500–1,000 kcal/day by use of a diet of 1,000–1,200 kcal/day for women and 1,200–1,400 kcal/day for men.[27]

The excessive weight particularly observed in patients with SLE on chronic corticosteroids determines a higher probability of cardiovascular diseases, generating a vicious circle, in which weight gain can maintain disease activity, requiring the continuation of corticosteroids.[22]

Table 1 shows the major favorable and unfavorable aspects regarding calories in the treatment of SLE. The major food sources indicated in Table 1 are found in the USDA National Nutrient Database for Standard Reference.[28]

Protein

Studies have shown that moderate-protein diet-fed mice had a long-lasting immune function and a delay in the autoimmunity development as compared with normal-protein diet-fed mice. A diet with restriction of the amino acids phenylalanine and tyrosine was beneficial to NZB/NZW mice.[8,20]

Supplementation with royal jelly (a honeybee secretion) has also been considered beneficial.[29] Its composition rich in free amino acids, simple carbohydrates, proteins, short-chain fatty acids, and vitamins causes a reduction in cholesterol and has immunomodulating and anti-inflammatory activities. In fact, the royal jelly supplementation has induced a reduction in the IL-10 serum levels and has increased the life span of NZB/NZW mice, suppressing the disease symptoms.[29]

In human beings, the study by Caetano et al.[8] has revealed that excessive protein intake causes a constant bone mineral loss in patients with juvenile SLE. On the other hand, the consumption of a protein-restricted diet (0.6 g/kg/day) has improved the glomerular filtration rate in the predialytic chronic kidney disease of patients with systemic diseases.[30] It is worth noting that, in lupus nephritis, a hypoprotein diet is not recommended to prevent negative nitrogen balance and malnutrition.[31]

Isoflavones

Because soybean-based foods have high levels of isoflavones, whose structure is similar to that of 17β-estradiol (E2), they have estrogenic effects and reduce proteinuria and the renal lesions associated with progressive renal failure.[17,32] However, potent adverse effects of isoflavones on the immune response of mice have also been reported.[33]

Zhao et al.[33] have reported that a soybean-rich diet can exacerbate renal damages, increasing serum creatinine and reducing the creatinine clearance, which increase the severity of the glomerular disease in MPL/lpr mice. The results have shown that soybean can accelerate glomerulonephritis, but improves the proliferative function of T cells.[33]

On the other hand, Hong et al.[32] have shown that the supplementation with isoflavones increased the survival of SLE murine models, inhibiting the production of autoantibodies (anti-dsDNA and anticardiolipin), and reducing the secretion of IFN-γ. Those authors have also reported that isoflavones have anti-inflammatory properties and antioxidant effects.[17,32]

L-canavanine

This non-protein amino acid can be found in grains (soybean), onion, seeds and sprouts of alfalfa (major source) and other plants. It is a natural L-arginine homologue that acts with antimetabolic activity and whose presence can result in cell apoptosis in conditions of arginine deficiency.[34] Studies have demonstrated that the L-canavanine amino acid acts as a suppressor-inductor of T cells that regulate the synthesis of antibodies and the proliferation of lymphocytes.[20]

Alfalfa sprouts have high levels of fibers and prevent hypercholesterolemia and atherosclerosis in some SLE models.[21] Hong et al.[17] have concluded that supplementation with ethylacetate extract of alfalfa in murine models for SLE reduced significantly the secretion of IFN-γ, reducing the inflammatory risk and immune mediators. However, some studies with human volunteers and healthy cynomolgus monkeys have shown that the intake of alfalfa sprouts can induce a lupus-like autoimmune syndrome (with antinuclear antibodies, anti-dsDNA, and complement reduction), and its discontinuation induces remission.[17,34]

The Baltimore Lupus Environmental Study (BALES) has also shown a significant association between alfalfa sprout consumption and the appearance of SLE, suggesting that none of its derivatives should be used.[22,34] In addition, in patients with SLE and inactive disease, the consumption of 8–15 tablets of alfalfa per day has been shown to reactivate the clinical symptoms of the disease and its serological aspects.[17]

Although the findings have suggested that alfalfa derivatives should not be used in SLE, it is worth noting that cooking and autoclaving apparently destroy their deleterious effects without damaging their lipid-lowering properties.[16]

Taurine

Taurine is the major free intracellular β-amino acid found in mammal tissues that can be synthetized through methionine and cysteine, being found mainly in foods, such as eggs, meat, oyster, and squid. Taurine exerts an important protective function, because, in addition to regulating the immune response, reduces oxidative stress, inflammatory cytokines, and apoptosis, and reduces the serum levels of lipids and their oxidation in mice.[35,36]

Huang et al.[35] have shown that taurine supplementation in NZB/NZW mice fed a hypercholesterolemic diet has reduced cardiac abnormalities, such as histopathologic changes, increased apoptosis, and fibrosis. Taurine has been commonly indicated for the treatment of myocardial failure, hepatic abnormalities

Table 1
Favorable and unfavorable aspects of calories, proteins and amino acids in systemic lupus erythematosus

Nutrient	Favorable	Unfavorable	Sources[28]
Calories	***Restriction*** Inhibits the reduction of $CD4^+$ and $CD8^+$ T lymphocytes and attenuates ↑ of Th1 (IL-2 and IFN- γ)[22] ↓ progression of autoimmune diseases[20] ↓ secretion of IgG 2A[17,21–23]	***Excessive consumption*** Metabolic syndrome Higher risk of cardiovascular diseases Disease activity[22] ↑ weight and obesity	Foods and/or preparations rich in simple carbohydrates and fat
Protein	***Moderate consumption*** Better immune function Delay in autoimmunity[8,20]	***Excessive consumption*** Greater bone mineral loss ↓ creatinine clearance in chronic renal failure in SLE (content > 0.6 g/kg/day)[30] ***Restriction*** Negative nitrogen balance in lupus nephritis Malnutrition[31]	Meat**, dairy products**, eggs**, pulses, whole cereals*
	Supplementation with royal jelly Immunomodulatory and anti-inflammatory effect ↓ cholesterol ↓ serum levels of IL-10 ↓ SLE symptoms (experimental)[29]	NA	
Isoflavones	Anti-inflammatory and antioxidant effects[17,32] ↓ autoantibody production (anti-dsDNA)[17,32] ↓ IFN-γ secretion ↓ proteinuria	↑creatinine[33]	Soybeans and derivatives**, dietary supplements, morning cereals*, black beans, olive oil*
L-canavanine	Prevents hypercholesterolemia (experimental)[17,34] ↓ cell apoptosis[34]	Lupus-like in humans Serologic reactivation[17,22,34]	Alfalfa**, seeds*, onion*, soybeans*
Taurine	Protective effect against free radicals[36] ↓ oxidative stress ↓ inflammatory cytokines and apoptosis[35] ↓ lipids and lipid oxidation (experimental)[35,37]	NA	Eggs**, meat**, oyster**

NA: information not available. *Sources with lower contents; **Major sources.

associated with SLE, and liver damages of patients with chronic hepatitis, when used at the dosage of 10 g/kg of weight in the diet of animals and 1 g/kg of weight for human beings.[35,36]

Several studies have shown the protective effect of taurine against free-radical damages, in addition to the inhibition of the hepatic apoptosis induced by biliary acids in mice. However, the mechanism of those effects have not been clearly established.[36]

Table 1 shows the major favorable and unfavorable aspects regarding proteins and amino acids in the treatment of SLE, and their major food sources according to the USDA National Nutrient Database for Standard Reference.[28]

Lipids

Lipids are important because they provide polyunsaturated fat to the tissues so that lymphocytes can exert their functions properly. Restriction of saturated fat and increase in the intake of unsaturated fat are recommended, because of the important role of unsaturated fat in the immune system and its response to cancer and infectious diseases.[18]

Dietary lipids influence the concentration and composition of plasma lipoproteins; saturated fats and omega-6 polyunsaturated fatty acid (ω-6 PUFA) can drastically affect autoimmune diseases in mice.[18,20] The total, saturated and monounsaturated fats are not associated with the appearance of DM.[37] The higher intake of polyunsaturated fats reduces the risk of DM, while that of trans fats increases that risk – however, its minimal consumption can reduce that risk in as much as 40%.[37] Halen et al.[38] have shown that a hyperlipid diet induces atherosclerosis in MRL/lpr and MRL/n mice.

On the contrary, food lipid restriction reduces the expression of immune complexes in glomerulonephritis and prolongs the life span of NZB/NZW mice.[21] In addition, dietary lipids can change the balance between Th1 and Th2 cells, favoring the development of autoimmune phenomena.[18,21]

ω-3 and ω-6 polyunsaturated fatty acids

The eicosapentaenoic (EPA) and docosahexaenoic (DHA) unsaturated fatty acids inhibit the enzyme lipoxygenase, reducing the production of inflammatory eicosanoids derived from the arachidonic acid. The DHA has a significant inhibitory action on the nuclear factor κB (NF-κB) and TNF-α, being even more potent than EPA.[39] In addition, DHA significantly reduces the serum levels of anti-dsDNA, regulates IgG renal deposits in NZB/NZW mice, and reduces IL-18.[40,41] Halade GV et al.[40] have reported a significant increase in the life span of NZB/NZW mice with the DHA and EPA supplementation. The α-linolenic acid (ALA), linoleic acid (LA), and gamma linolenic acid (GLA) have also shown a significant inhibitory action on TNF-α and on the IL-2 secretion.[20,21,23,37,39,42,43]

Some studies have reported that EPA can influence physiological processes, protecting against cardiovascular problems and inflammatory diseases, such as SLE.[44] On the other hand, ω-6 PUFA can exacerbate SLE by inducing the inflammatory mediators.[20,45] Fassett et al.[41] have shown that ω-6 PUFA increases serum creatinine in mice with renal ischemia. The diet therapeutic intervention with EPA and DHA (at the proportion of 3:1), along with calorie restriction, has shown an important anti-inflammatory effect on NZB/NZW mice as compared with a PUFA-rich or calorie-restricted diet, in isolation.[21,22,38,40,42] Other studies have demonstrated that the increase in ω-3 PUFA and calorie restriction have reduced the levels of TG, total cholesterol and LDL-C, in addition to reducing the severity of both autoimmunity and nephritis in NZB/NZW mice.[38] Murine models of SLE have shown that the reduction in the consumption of ω-9 monounsaturated fatty acid and the increase in ω-3 PUFA have potentiated the therapeutic effect.[46]

Supplementation with primrose oil can increase the life span of MRL/1pr, NZB/NZW, and BXSB mice, mainly because of its content of GLA (19%), from which prostaglandin E_1 (PGE_1), which has an anti-inflammatory action and reduces lymphocytic activity, is formed.[20,22]

Fish oil, known as one of the major sources of ω-3 PUFA, has anti-inflammatory and anti-autoimmune (due to inhibition of T and B lymphocytes) effects. In addition, it suppresses the activity of macrophages and the production of cyclooxygenase metabolites, being significantly beneficial to the clinical, immune, and biochemical status in animal and human models of SLE.[16,19,23,44,46,47] Supplementation with fish oil as the exclusive source of lipids reduces proteinuria and protects the kidneys against the deleterious effects of free radicals in NZB/NZW, BXSB, and MRL/lpr mice with lupus nephritis,[39,47] by inhibiting PI3K lipid kinase (an important target for reducing glomerulonephritis).[40] In addition to reducing anti-dsDNA levels, its major benefit in SLE is due to its effect on apoptosis.[22,41,43] Chandrasekar et al.[23] have shown that supplementation with fish oil improves glomerulonephritis in NZB/NZW females by reducing the transforming growth factor β (TGF-β), renal mRNA, and protein.

EPA is considered a potent anti-inflammatory agent because it reduces the production of interleukins (IL-1β and IL-6) and of TNF-α, by changing the phospholipid composition of the cell membrane, inhibiting the production and the receptor interaction of inflammatory cytokines.[16,20,21,23,39] It is worth noting that a daily dose of 6 g of ω-3 PUFA for 10 weeks can cause a decrease of 4.6 mmHg in systolic blood pressure and of 3.0 mmHg in diastolic blood pressure in patients with SAH.[41]

Flaxseed oil, with 70% of ω-3 PUFA in its composition and rich in ALA, is a good dietary complement, because it reduces proteinuria levels and preserves glomerular filtration, in addition to reducing anti-dsDNA and anticardiolipin antibodies in mice and suppressing the anti-β2-glycoprotein I in the experimental model of the antiphospholipid syndrome.[16,21,22] That effect has not been found with the supplementation of other oils, such as those from safflower, *Juniperus virginiana*, fish, corn, and soybean, suggesting that the flaxseed oil has another protective component not completely identified, besides ω-3 PUFA.[16,18] Flaxseed can also inhibit the platelet activating factor, commonly elevated in the inflammatory response of patients with SLE.[20] It should be consumed in its whole form.[20] The daily dosage of 30 g proved to be benefic to reduce serum creatinine in patients with lupus nephritis, in addition to promoting a reduction of 11% in total cholesterol levels and of 12% in LDL-C levels.[16]

Table 2 shows the major favorable effects regarding specific foods, sources of ω-3 PUFA, in the treatment of SLE. In healthy human beings, dietary supplementation with ω-3 PUFA causes a reduction in the production of IL-1α, IL-1β, IL-2, IL-6, NF-κB, and TNF-α.[21,40] Several clinical studies have also shown that the consumption of ω-3 PUFA delays renal disease progression by reducing inflammation.[39] A study with 12 patients with lupus nephritis and supplemented with

Table 2
Major favorable effects of omega-3 food sources on systemic lupus erythematosus

Omega 3 food sources	Favorable effects
Fish oil	↓ triglycerides[16,22,38] ↑ HDL-C[16,22,38] ↓ total cholesterol and LDL-C[38] ↑ hepatic peroxidase (experimental)[39]
Flaxseed oil	↓ anticardiolipin and suppression of β-2 glycoprotein I[16,21,22] ↓ creatinine in lupus nephritis[16] ↓ total and LDL-C[16]
Flaxseed	Inhibition of platelet activity[20]

Table 3
Favorable and unfavorable aspects of lipids and polyunsaturated fatty acids in systemic lupus erythematosus

Nutrient	Favorable	Unfavorable	Sources[28]
Lipids	***Unsaturated*** Improve the immune system[18,20] Restriction leads to ↓ immune complexes[21] ***Polyunsaturated*** ↓ risk of DM[37]	***Saturated*** Aggravate AID[18,20] Dysregulate the Th1 and Th2 balance[18,21] ***Trans*** DM[37] ↑ atherosclerosis (experimental)[38]	***Polyunsaturated*** Vegetal oil**, oilseeds, fish**, soybean** ***Saturated and trans+*** Fried foods+, fast foods+, crustaceans, whole-fat dairy products, sausages+, egg yellow, pork meat, viscera
Omega 3	Protect against free radicals[22,41,43] Apoptosis[22,43] Anti-inflammatory effect[16,19-21,23,44,47] Cardiovascular protection in SLE[43] ↓ proteinuria[22,41,43] ↓ blood pressure[41] ↓ anti-dsDNA[22,41,43] ↓ leukotriene B4[16,22] ↓ IL-1α, IL-1β, IL-6[21,43] ↓ IL-2[20,21,23,37,39,42,43] ↓ TNF-α[20,21,23,37,39,42,43] ***DHA*** > antithrombotic effect [39,41] ↓ TNF-α and NF-κB[40] ↓ IL-18[40] ↓ anti-dsDNA[40] ↓ renal IgG deposits[40] ***EPA/DHA*** Supplementation leads to SLE remission[42] ↑ superoxide dismutase[42] ↑ glutathione peroxidase[42]	NA	Fish oil**, Flaxseed oil**, Primrose oil, Canola oil**, Soybean oil, Olive oil**, Nuts, Salmon**, Herring**, Sardine**, Tuna**
Omega 6	NA	SLE exacerbation[20,45] ↑ inflammatory mediators[20,45] ↑ creatinine (experimental)[41]	Corn oil**, sunflower oil**, soybean and flaxseed oils, milk*, eggs*, nuts*

DM: diabetes mellitus; AID: autoimmune diseases; NA: information not available. *Sources with lower contents; **Major sources; + Consumption not recommended.

fish oil (180 mg of EPA and 120 mg of DHA) has reported a reduction in the following: arachidonic acid; inflammatory status; platelet aggregation; blood viscosity; and leukotriene B_4.[22] It is worth noting that high doses (18 g/day) of fish oil reduce TG by 38% and increase HDL-C by 28%.[16,22]

Patients with SLE have a reduced concentration of GLA, ALA, EPA, and DHA in the phospholipid fraction, in addition to reduced levels of nitric oxide, which increase when those patients are supplemented with EPA/DHA.[42] Mohan et al.[42] and Pestka et al.[39] have reported a significant increase in the levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase and an increase in the hepatic catalase levels of NZB/NZW mice with the EPA/DHA supplementation, inducing SLE remission and being beneficial in the treatment of lupus nephritis with cyclophosphamide.[39,42,46] *In vitro* studies have revealed that the supplementation with GLA or arachidonic acid inhibits the production of IL-2. On the other hand, EPA has shown less inhibition of IL-2, indicating the immunosuppressive role of the ω-3 PUFA.[43]

Table 3 shows the major favorable and unfavorable aspects regarding lipids and fatty acids in the treatment of SLE, and their major food sources according to the USDA National Nutrient Database for Standard Reference.[28]

Vitamins

Vitamin A

The metabolites of vitamin A, such as retinoic acid, have an antineoplastic and regulatory role in cell proliferation and differentiation, in addition to increasing T cell cytotoxicity and proliferation and manifesting significant defects in Th cell activity.[19,48] They also have therapeutic effects on several animal models of renal diseases, such as lupus nephritis.[48]

The study by Ikeda et al.[49] with MRL mice has shown that vitamin A derivatives, such as etretinate (synthetic retinoic acid) and retinoids, have significantly reduced dermal thickening and proved to be therapeutic agents in cutaneous T cell lymphoma and cutaneous basal cell carcinoma,

because of their apoptosis-inducing action. Those mice, treated with 5 mg/kg and 10 mg/kg of etretinate, have not even had the characteristic cutaneous and dermatological lupus-like lesions, probably due to its suppressive effect on cytokine expression.[49]

Other recent studies have shown that retinoids inhibit the formation of proinflammatory Th17 cells and promote the production of anti-inflammatory regulatory T cells in murine models of autoimmune diseases.[15] Kinoshitak et al.[48] have shown that patients treated with retinoids improved their proteinuria, their high levels of anti-dsDNA, and low titers of complements, with no side effects, suggesting that retinoids can be promising for the treatment of lupus nephritis.

The supplementation of vitamins A and D in patients with SLE can be indicated. The dose of 100,000 IU of vitamin A for two weeks has proved to be beneficial for the increased antibody-dependent cell cytotoxicity, activity of natural killer cells, and IL-2 response.[16] However, the consumption of extremely high doses of vitamin A (> 100,000 IU) can result in symptoms such as anemia, headache, dry skin, alopecia, nausea, anorexia, pseudo hydrocephalus, and death. On the other hand, the deficiency of vitamin A in experimental models of SLE has shown greater severity of symptoms. The researchers have attributed that fact to the increase in hypergammaglobulinemia and presence of autoantibodies.[20]

Vitamin D

Vitamin D, an important nutrient due to its multiple immunomodulating effects, is produced in the skin and obtained from food. The effects of its active form [$1,25(OH)_2D_3$] on immune response occur due to the inhibition of the proliferation of T lymphocytes (Th1).[47,50] The treatment of CD4 T cells with $1,25(OH)_2D_3$ inhibits the proliferation of Th1 cells and the production of cytokines, reduces the secretion of IL-2 and IFN-γ by the CD4 T cells, and promotes the production of IL-5 and IL-10, determining a shift toward a Th-2 response.[50]

The high consumption of vitamin D (≥ 37 ng⁄mL) has been associated with the reduction in the risks for type I DM, autoimmune encephalomyelitis, SAH, hypertriglyceridemia, MS, inflammatory bowel disease, SLE, and multiple sclerosis.[51–53] A recent prospective study carried out with 18,000 women during 22 years has found no association between vitamin D intake and risk for SLE, disagreeing with the hypothesis that the high vitamin D intake would be associated with protection against SLE.[51] However, other epidemiological evidence supports the association between vitamin D and the severity of those autoimmune diseases.[53]

Patients with SLE have been shown to have several factors that reduce vitamin D levels (≤ 20 ng⁄mL), which does not occur with patients with rheumatoid arthritis (RA) and osteoarthritis.[16] One possible explanation for the reduction in vitamin D levels in SLE is the intense photoprotection of those patients,[16,50,51,53,54] in addition to the relative hypoparathyroidism caused by the high IL-6 levels (mainly in disease activity) and the chronic use of steroids, which changes its metabolism leading to the formation of biologically inactive metabolites and decreasing calcium absorption.[50,55,56] Some studies have also suggested that excessive weight is an important risk factor for vitamin D deficiency in SLE.[50,55,56]

In addition to those factors, hydroxychloroquine seems to reduce the conversion of vitamin D_2 into D_3, its biologically more active form. Antibodies antivitamin D have also been described in patients with SLE, being associated with anti-dsDNA antibodies, present during disease activity.[50,53] It is worth noting that low levels of 25(OH)D are related to the highest scores of inflammatory activity in SLE (SLEDAI);[53] on the other hand, its high levels (> 36.8 ng/mL) are associated with greater bone mineral density (both in young and elderly individuals of both genders), according to data of the Third National Health and Nutrition Examination Survey.[57]

Recent reviews have confirmed that patients with SLE have significantly low serum levels of 25(OH)D (close to 25.5 ± 12.1 nmol/L), while the minimum serum concentration recommended is 50–80 nmol/L.[50,52,55,57] Supplementation of that vitamin is appropriate, because its better indicator [$1,25(OH)_2D_3$] also plays a role in calcium homeostasis and immune regulation.[16,54,55,57] Supplementation with vitamin D_3 in MRL/lpr mice has yielded longevity, a reduction in proteinuria, improvement in bone health and a positive impact on immunity.[50,52,58]

Vitamin E

The combination of fish oil and vitamin E has an impact on several SLE mediators. Mice fed with fish oil and 75 IU of vitamin E showed a reduction in inflammatory cytokines, PGE_2, leukotriene B_4, and thromboxane B_2, to which a reduction in the following factors was added with the increase in vitamin E offer to 500 IU: IL-6; IL-10; IL-12; and TNF-α.[16,47] The significant effects on IL-2, IL-4, and TNF-α, obtained through the supplementation with vitamin E and ω-3 PUFA, have suggested that oncogenic levels can be delayed.[43]

Some studies with MRL/lpr mice have shown that treatment with vitamin E supplementation modulates the levels of inflammatory cytokines, delays the appearance of autoimmunity, and increases survival,[15] but the treatment in patients with SLE is still controversial.[20] Other studies have found effects of vitamin E supplementation on neither endothelial dysfunction nor lipid peroxidation.[59]

Another factor to be considered regarding not only vitamin E, but also vitamin A and β-carotene, supplementation relates to the reduction in the levels of the antioxidants α-tocopherol, β-carotene and retinol found in patients with SLE and RA, suggesting important damage to the inflammatory process caused by free radicals.[15,16] The adequate consumption of vitamins A and E is inversely related to the SLE activity, according to Minami et al.[45] However, the recent study by Costenbader et al.[15] has not supported the existence of a relationship between consumption of food antioxidants or supplements and the risk for developing RA or SLE in women.

Vitamin B complex

The study by Varghese et al.[60] in mice has shown that immune therapy with folate minimizes the symptoms of SLE and prolongs life span.

The higher plasma levels of homocysteine might be associated with atherosclerosis in SLE, which reinforces the need for a higher consumption of vitamins B6 and B12 (in addition to folate), which are important cofactors in its metabolism and promote a reduction in homocysteine levels.[61] In addition, those vitamins also influence the serum levels of some inflammatory markers, such as cytokines and C-reactive protein (CRP).[61]

Some studies have shown that the consumption of vitamin B12- and folate-deficient diets has caused a plasma increase in homocysteine in patients with SLE. Thus, it has been suggested that patients on a hypolipid diet (indicated for SLE) should increase their consumption of cereals fortified with those nutrients, in addition to vegetables and fruits. The possibility of supplementation should also be considered.[62]

The study by Minami et al.[61] has shown the association of high doses of vitamin B6 and folate with a lower severity of SLE in Japanese patients, regardless of the non-dietary factors. The studyby Ardoin et al.[63] has shown that niacin reduces TG and LDL-C levels by 23% and 30%, respectively, in children with dyslipidemia, although it does not significantly affect HDL-C levels.

Vitamin C

Studies with mice have suggested that vitamin C reduces IgG and anti-dsDNA levels and that its insufficient consumption can maintain oxidative stress and induce inflammation in the active phase of disease.[45]

According to the study by Minami et al.,[45] carried out with 279 patients with SLE, vitamin C consumption is inversely associated with the risk of SLE inflammatory activity. The antioxidant properties of that vitamin modulate the immune functions and release of inflammatory mediators.[45] Tam et al.[59] have shown that the supplementation with antioxidants is a potent therapy to prevent cardiovascular complications. In fact, monthly vitamin C supplementation has determined a significant improvement in the mediation flow of vasodilation in patients with coronary artery disease.[59] The safe maximum dose is 1 g/day, because the consumption of higher doses determines the appearance of ascorbate in urine. The combination of daily supplementation of vitamin C (500 mg) with vitamin E (800 IU) for three months was associated with a small reduction in lipid peroxidation, without affecting other markers of oxidative stress or endothelial function in patients with SLE.[59]

Table 4 shows the major favorable and unfavorable aspects regarding vitamins for the treatment of SLE, and their major food sources according to the USDA National Nutrient Database for Standard Reference.[28]

Fibers

Adequate intake of dietary fibers is recommended, because it lowers post-prandial glycemia and lipids, yielding low-energy-density nutrients. In addition, dietary fibers improve intestinal constipation, promoting satiety due to the longer chewing time.

Epidemiological studies have reported that fibers protect against cardiovascular diseases.[64,65] In fact, 10 cohort studies in the United States and Europe, with a six-to-ten-year follow-up, have concluded that fibers were associated with a risk reduction of 14% and 27% in coronary events and coronary death, respectively.[65] Those results can be explained by the effect of fibers on blood pressure and on CRP levels. The intake of fibers has been inversely associated with CRP in the National Health and Nutrition Examination Survey 1999–2000.[66]

As foods are digested and absorbed in the small intestine, the fibers increase the viscosity in the intestinal lumen, interfering with the biliary acid absorption from the ileum. The LDL-C is removed from the blood and converted to biliary

acids to replace those eliminated with defecation. This change in the pool of biliary acids, along with the intake of viscous fibers, depress cholesterol synthesis.[61,64] Simultaneously, inulin, oligosaccharides, resistant starch, and other fibers increase mineral absorption, especially that of calcium.[67]

The diet therapeutic intervention to control hypercholesterolemia and MS in SLE should emphasize the importance of consuming fiber-rich foods, especially the soluble ones (found in oat, fruits and pulses) to control dyslipidemia.[62] The recommendation is 14 g of fibers per 1,000 kcal consumed (or 38 g for men and 25 g for women), adequate fluid ingestion being required.

Minami et al.[61] have also reported that fiber intake was inversely proportional to the SLE severity risk. Some studies has already shown that fiber intake is inversely associated with the plasma levels of homocysteine and of the inflammatory markers IL-6 and CRP.[61] However, excessive fiber intake reduces the absorption of vitamins, minerals, protein and energy.[64]

Table 4 shows major favorable and unfavorable aspects regarding dietary fibers for the treatment of SLE, and their major food sources according to the USDA National Nutrient Database for Standard Reference.[28]

Minerals

Zinc

MRL/lpr mice on a zinc-restricted diet have shown a reduction in lymphoproliferation and in anti-dsDNA titers, and an improvement in glomerulonephritis, as well as a reduction in the production of autoantibodies in NZB/NZW models.[21]

A zinc-restricted diet determines an increase in the serum levels of corticosteroids, which can contribute to control SLE.[20] On the other hand, a study in human beings has shown that zinc deficiency causes an immune dysfunction that affects mainly Th cells, and can cause neurosensorial disorders and body mass reduction.[19]

Selenium

A diet rich in selenium, a natural antioxidant, increases anti-inflammatory properties, with a reduction in anti-dsDNA antibodies, improving the activity of natural killer cells and survival in murine models of SLE.[16,20,47] It can have a significant effect on the maturation of T cells and on the response of T cell-dependent autoantibodies.[19]

Calcium

An adequate consumption of calcium is extremely important in SLE, particularly in patients with a reduction in bone mineral density either associated or not with corticotherapy and regardless of disease duration.[62,68] The risk of osteoporosis is greater due to disease activity, vitamin D deficiency, non-exposure to sunlight, and early menopause caused by cytotoxic agents.[54,68] In fact, women with SLE are five times more likely to undergo fractures as compared with healthy women of the same age.[62]

The American College of Rheumatology (ACR) has issued recommendations to reduce bone mass loss in patients with SLE treated with corticosteroids. In addition, ACR has suggested that patients receiving more than 5 mg of prednisone daily, for three months, should begin to receive calcium and vitamin D prophylactically, and undergo assessment of bone density and of the use of other medications. Changes in life style and a calcium-rich diet have also been suggested.[20,62,68] Supplementation of calcium (> 1,500 mg) and vitamin D (20 μg or 800 UI) is indicated in cases of difficulty in obtaining those nutrients from the diet.[20,58]

Iron

Some studies have suggested that iron can cause cell damages and that the use of chelating agents has shown benefits in experimental models for autoimmune diseases. More severe renal lesions were more prevalent in mice being supplemented with iron as compared with controls; however, animals with mineral deficiency developed more severe clinical signs of the disease. That study has suggested that a dietary restriction would reduce mortality in those models.[69]

On the other hand, some studies with patients with SLE have shown that anemia can be detected in up to 70% of them during the course of disease. The most often found type of anemia is that of chronic disease (characterized by deficient mobilization of iron to the bone marrow, despite the normal or increased values of iron reserves).[70] In the case of iron-deficiency anemia, the consumption of the following is indicated: lean meat (mainly white); dark-green leafy vegetables; whole cereals; iron-fortified foods; and, in more severe cases, medicamentous supplementation.[62]

Sodium

Patients with lupus nephritis and those with SAH, either secondary or not to corticotherapy, need to follow a sodium-restricted diet. The daily amount considered adequate and safe for those conditions is of 3 g sodium/day, and should be also followed by a restriction of fluid intake (maximum of 1.5 L/day).[31]

Copper

High serum concentrations of copper have been observed in patients with SLE and RA, and such levels are directly related

Table 4
Favorable and unfavorable aspects of vitamins, fibers and minerals in systemic lupus erythematosus

Nutrient	Favorable	Unfavorable	Sources[28]
Vitamin A	***Retinoids*** Antineoplastic agent[48] Induces apoptosis[49] ↓ proteinuria and improves hypoalbuminemia[48] ***Supplement*** ↑ natural killer cell activity and response to IL-2[16]	***Very high doses*** Anemia, headache, dry skin, alopecia, nausea, anorexia, pseudo hydrocephalus and death[20]	Carrot**, pumpkin**, sweet potato, spinach, kale, liver
Vitamin D	Immunomodulatory effects[16,55] Inhibition of Th1 proliferation Calcium homeostasis[16,55,57] ↓ IL-2, IFN-γ[50] and ↓ proteinuria[50,52,58] ↑ IL-5 and IL-10[50] ***High intake*** ↓ risk of type 1 DM, SAH, SLE[51–53]	***Reduction in 25(OH)D*** Associated with high SLEDAI scores[53]	Foods fortified with vitamin D**, salmon, sardine, tuna, eggs, liver
Vitamin E	***Adequate intake*** Inversely related to SLE activity[45] ***Supplementation*** Delay in oncogenic levels[43] Delay in autoimmunity[20] ↓ cytokines, PGE_2, leukotriene B_4, thromboxane B_2 ↓ IL-6, IL-10, IL-12 and TNF-α[16,47]	NA	Whole cereals**, nuts**, fish**, sunflower seeds, spinach, vegetal oils, soybean milk, margarine*
Vitamin B complex	***B6 and B12*** ↓ homocysteine[61] ***Folates*** Minimizes SLE symptoms[60,61] ***Niacin*** ↓ triglycerides and LDL-C[63]	***Deficiency of B12 and folate*** ↑ homocysteine in SLE[62]	Red meat**, liver**, fortified cereals**, chicken, salmon, sardine
Vitamin C	Antioxidant Immune function modulator Release of inflammatory mediators[45] ↓ IgG and anti-dsDNA[45]	***Insufficient intake*** Induces inflammation[45] ↑ oxidative stress	Orange juice**, tangerine**, papaya**, broccoli**, whole cereals, tomato
Fibers	Low-energy-density Protection against cardiovascular diseases[64] Better control of hypercholesterolemia[62] Lower chance of metabolic syndrome[62] ↓ post-prandial glycemia and lipids ↓ blood pressure and CRP[61,66] ↓ homocysteine and IL-6[61]	***Excessive intake*** ↓ absorption of vitamins, minerals and protein[64]	Whole cereals**, pulses**, vegetables, fruits (papaya, orange, plum)
Zinc	***Restriction*** ↓ anti-dsDNA titers ↓ autoantibodies (models)[21] ↓ symptoms of autoimmune diseases[20]	***Deficiency*** Immune dysfunction Neurosensorial disorders ↓ body mass[19]	Mollusks**, white beans, turkey, lamb, milk*, soybean*, seeds, spinach*
Selenium	Antioxidant Anti-inflammatory Improves the activity of natural killer cells Longer survival in SLE (experimental)[16,20] Important in T cell maturation[19]	NA	Nuts**, whole cereals**, fish (tuna, haddock, salmon), chicken, mollusks, fortified flours and products, ricotta*, Egg*, sunflower seed
Calcium	Important in bone mass reduction[54,62,68]	NA	Dairy products**, kale**, spinach**, sardine**, fortified whole cereals, soybean*
Iron	Anemia prevention[70]	***Supplementation*** Worsens renal damages ***Deficiency*** Worsens SLE clinical findings[69]	Mollusks**, fortified whole cereals**, meat**, soybeans*, pulses*, spinach, broccoli, kale
Sodium	NA	SAH Lupus nephritis Fluid retention[31]	Salt** and industrial condiments+, preserves**, canned foods**, salty snacks+, cheeses w/ salt, sausages+
Copper	Possible therapeutic effect on inflammatory diseases[46]	NA	Viscera** (liver**), beans, lentils

NA: information not available. *Sources with lower contents; **Major sources; +Consumption not recommended.

to disease activity and probable inflammatory response. Copper is believed to exert a therapeutic effect on the treatment of chronic diseases because its liver storage is insufficient to meet the demands of the inflammatory response. Exogenous copper reduces cell formation in mice, but its supplementation has not produced significant serum changes in the study by Duffy et al.[46]

Table 4 shows major favorable and unfavorable aspects regarding minerals for the treatment of SLE, and their major food sources according to the USDA National Nutrient Database for Standard Reference.[28]

CONCLUSION

Considering all favorable and unfavorable aspects of the major nutrients, it is safe to state that the adequate diet for the treatment of SLE is mainly aimed at reducing the risk for cardiovascular and atherosclerotic diseases, in addition to reducing the inflammatory factors and improving the immune function. Patients with SLE can benefit from a nutritionally balanced diet for maintaining the ideal body weight, with effective calorie control to avoid insulin resistance, increasing HDL-C (protective) levels and reducing TG levels.

The patient with SLE should be instructed to follow a calorie-restricted diet to prevent and/or treat excessive weight, in addition to a diet with a moderate protein content, isoflavones being indicated for protein supplementation, but L-canavanine, which aggravates SLE symptoms, being contraindicated. Regarding the lipids in the diet, a greater offer of mono- and polyunsaturated fatty acids is recommended in daily meals, due to their anti-inflammatory and cardiovascular protective functions. Supplementation with ω-3 PUFA can be suggested due to its countless benefits. On the other hand, the restriction of ω-6 PUFA and other sources of saturated and trans fatty acids in the diet should be enforced, because of their pro-inflammatory effects and aggravating effects for cardiovascular diseases, respectively.

It is worth noting the importance of offering vitamins, mainly vitamin D, fibers and minerals, such as calcium and selenium. On the other hand, the sources of zinc and sodium should be restricted to prevent possible disease aggravation. Thus, the major recommendations of diet therapy (Table 5) are intended to provide better quality of life to patients with SLE and more safety in the course of their treatment.

Table 5
Most indicated nutrients for the treatment of systemic lupus erythematosus, favorable and unfavorable aspects of consumption and food recommendation

Nutrient	Favorable	Unfavorable	Recommended[28]
Polyunsaturated fatty acid (ω-3)	++	-	Oils of flaxseed and canola, fish oil, olive oil, salmon and sardine
Fibers	++	-	Whole cereals, pulses
Isoflavones	++	?	Soybeans and derivatives
Vitamin D	++	?	Vitamin D-fortified foods
Taurine	+	-	Eggs, meat
Vitamin A	+	-	Carrot, pumpkin
Vitamin E	+	-	Whole cereals, nuts, fish
Vitamin B complex	+	-	Red meat, fortified cereals
Vitamin C	+	-	Orange juice, tangerine, broccoli, papaya
Selenium	+	-	Nuts, whole cereals
Calcium	+	-	Dairy products, kale, sardine, spinach

+ Evidence; ++ Strong evidence; - Negative evidence; ? No data.

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