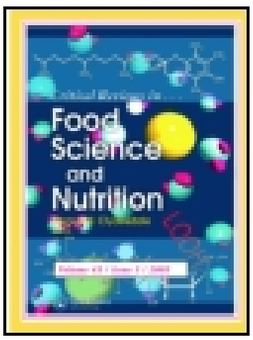

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DIETARY INTERVENTION AND HEALTH IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW OF THE EVIDENCE

Marília Cristina Santos de Medeiros[1], JUSSARA CRISTINA ALVES MEDEIROS[1], HUMBERTO JEFFERSON DE MEDEIROS[1], JOSÉ CARLOS GOMES DE CARVALHO LEITÃO[2], and MARIA IRANY KNACKFUSS[1]

[1]Universidade do Estado do Rio Grande do Norte, Mossoro, 59610-210 Brazil

[2]Universidade de Tras-os-Montes e Alto Douro Escola de Ciencias da Vida e do Ambiente, Vila Real, 5000-801 Portugal

ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the scientific evidence of dietary intervention, either through diet or supplementation, and its effects on the health of patients with systemic lupus erythematosus. METHODS: Literature searches were conducted using Scopus, PubMed, BioMed Central and Science Direct databases. The terms used for the search were diet, nutritional support, nutrition therapy and systemic lupus erythematosus. RESULTS: Eleven studies with interventions related to supplementation of omega-3 fatty acids, vitamin D and turmeric, as well as changes in diet composition, such as low glycaemic index diet were identified. CONCLUSIONS: The studies evidenced that omega-3 supplementation reduced

inflammation, disease activity, endothelial dysfunction and oxidative stress; vitamin D supplementation increased serum levels, reduced inflammatory and hemostatic markers; turmeric supplementation reduced proteinuria, hematuria and systolic blood pressure; and low glycaemic index diet caused weight loss and reduced fatigue.

Keywords: Diet; Nutrition support; Nutrition therapy; Systemic lupus erythematosus; Intervention.

INTRODUCTION

Autoimmune diseases are among the most challenging scientific and clinical problems of immunology (Abbas, Lichtman, and Pillai 2015). The development of systemic lupus erythematosus (SLE) is linked to genetic predisposition and to environmental factors, such as ultraviolet light and some medications (Brazilian Society of Rheumatology 2004).

Some of the manifestations present in the SLE patient are related to nutrition, not as an etiological factor, but as clinical repercussion. The most common include selenium, zinc and vitamin D deficiency, lipid change, anorexia, pancreatitis, hepatitis, nephritis and glomerulonephritis (Klack, Bonfa, and Borba Neto 2012, Sahibari et al. 2014). It should be noted

that chronic corticosteroid therapy also causes side effects that can be minimized through diet therapy. The main effects of corticosteroid therapy are weight gain, high blood pressure, osteoporosis, dyslipidemia, hypokalemia, hyperglycemia and insulin resistance and predisposition to infections (Mocarzel 2015).

The overall aim of the SLE therapy is to control disease activity. The ability to measure disease activity also facilitates the management of the disease in patients, because severe disease activity at presentation is a prognostic factor associated with mortality. Thus, some instruments are developed because they are essential for a standardized assessment of the disease activity. The main instruments used are Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index), SLAM (Systemic Lupus Activity Measure), SDI (Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index) (Aparicio-Soto, Sánchez-Hidalgo, and Alarcón-de-la-Lastra 2017).

These instruments can also be used to evaluate the effects of the treatment, with drug or non-drug therapies, particularly diet. Patients with SLE can benefit from nutrition through the use of immunomodulatory and anti-inflammatory foods, which improve lipid profile, delay the progression of kidney disease when it occurs and optimize weight control with subsequent control of high blood pressure and insulin resistance. In this respect, it was necessary to address in this systematic review (SR) the studies that reveal the dietary intervention performed in patients with SLE and what are their beneficial impacts on the health of these people, guiding the conduct of the professionals who take care of their diet.

It is not clear the various mechanisms of action of these dietary factors and to determine recommendations for dosing and frequency of consumption. However, the data available until now are sufficient do determine that these factors constitute a novel and under-explored aspect of autoimmunity that will hopefully inspire further investigation, since several dietary elements are involved in disease progression or prevention (Dahan, Segal, and Shoenfeld, 2017).

The purpose of the present study was to evaluate the scientific evidence of dietary intervention, either through diet or supplementation, and its effects on the health of SLE patients.

MATERIALS AND METHODS

Search strategy and data sources

The present SR was performed observing the methodological procedures of The Cochrane Collaboration (Scholten, Clarke, and Hetherington 2005). The searches were carried out in Scopus, PubMed, BioMed Central and Science Direct databases from August to December 2016. Based on the terms Mesh and Boolean Operators, the following search strategy was performed: diet* OR "nutritional support" OR "nutrition therapy" AND "systemic lupus erythematosus".

The studies were independently analyzed by two reviewers, MCSM and JCAM. First the papers were excluded based on title and abstract. The full text was obtained for the reading and application of inclusion and exclusion criteria (Figure 1). Reviewers extracted from the studies information about the author, year of publication, country, participants and intervention characteristics and duration of the treatment (Table 1).

Inclusion and exclusion criteria

Original articles were included with dietary intervention, either for food or supplements, in adults with SLE (18 to 59 years), in both sexes, published between 2006 and 2016, in English, Spanish or Portuguese. The studies should report on the intervention performed and the effects on the health status of SLE patients.

Studies were excluded because: a) animal experiments, b) patients with other types of lupus, c) studies evaluating only serum nutrient analysis or dietary intake.

Methodological quality assessment

The selected studies were critically appraised using the checklist Downs & Black (Downs and Black 1998). The checklist was applied independently by two reviewers, and when there were differences in the classification of articles, a third reviewer was consulted. We used the checklist Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA), thus following the requirements determined for the elaboration of a SR.

RESULTS

Initial searching 11.450 articles were identified. Then, 7.397 articles were excluded by the filters applied at each base. Following the screening process, 4.039 articles were excluded by duplicates and by reading the title and abstract, leaving 14 studies for the complete reading. Of

these, only 10 studies were included in the SR, but another study was included because it was in the references of one of the selected studies and met the inclusion and exclusion criteria of this study, totaling 11 studies analyzed in this SR* (Figure 1).

The data presented in Table 1 refer to the characteristics of the studies included in the SR. All research was experimental and the sample size ranged from 9 to 267 people, with some studies being for females only, others for both sexes. The mean age ranged from 29 to 50 years.

DISCUSSION

It was observed that nutritional support research in the SLE population is focused on intervention mainly with omega-3 and vitamin D. We also found a study that involved turmeric intervention, and a study that analyzed the effect of low glycaemic index diet compared to a low calorie diet. The outcomes were inflammatory markers, endothelial dysfunction, lipid changes and consequent risk of developing cardiovascular disease, vitamin D deficiency, fatigue and reduced quality of life (Table 1).

Omega-3 and SLE

The research on omega-3 supplementation in SLE patients is due the recognized anti-inflammatory action of this nutrient. These fatty acids are essential for the synthesis of eicosanoids, which are mediators and regulators of the inflammatory cascade. They control inflammation by reducing the levels of CRP, cytokines, chemokines and other inflammatory

mediators (Bhangle and Kolasinski 2011, Li et al. 2014, Schwab and Serhan 2006, Wallace, Miles and Calder 2003).

Metabolomics studies have shown reduced levels of omega-3 in SLE patients compared to healthy subjects (Wu et al. 2012). The observation of this deficiency has led to several clinical trials using fish oil supplements and evaluating their impact on different health outcomes, such as serum levels of cytokines and adipokines, CRP, glycemia, lipid profile, quality of life, disease activity, endothelial dysfunction and oxidative stress markers (Borges et al. 2016, Arriens et al 2015, Bello et al. 2013, Wright et al. 2008).

The study by Borges et al. 2016 with fish oil supplementation observed that there was no impact on serum levels of IL-6, IL-10, leptin and adiponectin, although a significant decrease of CRP concentrations was observed.

The clinical trial conducted by Arriens et al. 2015 identified improvement in the vitality and emotional well-being subscale of SF-36 in the omega-3 group when compared to the placebo group. The authors observed that supplementation promoted improvement in disease activity assessed by PGA, but did not identify the same result in disease activity as assessed by SELENA-SLEDAI and renal SELENA-SLEDAI. With regard to outcomes related to systemic inflammation, supplementation showed a significant reduction in the erythrocyte sedimentation rate and, among the cytokines evaluated, IL-13 increased and IL-12 reduced in both groups.

The research conducted by Wright et al. 2008 and Bello et al. 2013 had as analyzed endpoints the endothelial dysfunction and the disease activity after fish oil supplementation.

Endothelial dysfunction is present in several metabolic and/or vascular diseases, such as obesity, diabetes mellitus (DM), high blood pressure and dyslipidemia, which are marked by

insulin resistance, which in turn has been strongly associated with early endothelial dysfunction (Mombouli and Vanhout 1999, Ferrannini et al. 1997, Hsueh, Lyon, and Quiñones 2004). It is measured by means of flow-mediated dilatation of the brachial artery (FMD) based on the capacity of nitric oxide released by the endothelium after ischemic stimulus, which promotes arterial dilatation. It allows early detection of dysfunction, providing prophylactic therapy and consequent reduction of health problems resulting from this alteration (Raitakari and Celermajer 2000).

In SLE patients, studies have confirmed the presence of subclinical vascular disease, with compromised arterial compliance in these subjects (Roman et al. 2003, Bruce et al. 2003, Asanuma et al. 2003). Based on this finding, the authors hypothesized that omega-3 supplementation in patients with SLE could confer vascular protection through an improvement in endothelial function and reducing in stress oxidative (Wright et al. 2008).

Then, Wright et al. 2008 observed a significant decrease in the levels of platelet 8-isoprostanes in both groups. They also observed a reduction on disease activity assessed by SLAM-R and BILAG in the supplemented group, but not in the placebo group. FMD increased in the fish oil group and, at the end of the 24 weeks of intervention, a positive correlation was observed between percentage EPA and percentage DHA in the platelet cell membranes and the degree of FMD.

Bello et al. 2013 when analyzing the same outcome that Wright et al. 2008 found quite different results. The authors did not observe differences between the omega-3 supplemented group and the placebo group on endothelial dysfunction, disease activity and inflammatory markers such as IL-6, ICAM-1 and VCAM-1. The authors were unable to explain why these

results were so different from Wright et al. 2008, because even with 12 weeks of intervention, they already noticed a decrease in endothelial dysfunction, disease activity with a significant reduction in SLAM-R and BILAG.

Finally, in relation to EPA and DHA supplementation, it has been suggested that they do no act synergistically to improve all aspects of vascular function. Thus, it may the relative amounts of EPA and DHA within the supplement that determines what vascular improvement is observed; however, this requires further study (McVeigh et al. 1994, Morgan et al. 2006, Mori et al 2000). In addition, the more concentrated EPA and DHA the fish oil is, the fewer capsules will be required per day, which may facilitate adherence to treatment.

Vitamin D and SLE

Vitamin D was another supplement that was the focus of research in clinical trials. This is because the immune cells have vitamin D receptors, including B and T cells and antigen-presenting cells (Aranow et al 2015).

Vitamin D obtained by diet and mainly by sunlight exposure is converted to the hormone 1,25-dihydroxycholecalciferol (1,25 $[OH]_2$ D_3), and this is recognized mainly for its action on calcium homeostasis and bone health. However, the immune cells express enzymes required to convert vitamin D into its biologically active form (Adorini and Penna 2008).

In vitro, studies have demonstrated vitamin D modulates innate and adaptative immune responses, blocks B cell proliferation and differentiation and suppresses immunoglobulin

production. Additionally, it decreases T cell proliferation and shifts maturing T cells away from Th1 or Th17 phenotypes toward Th2 and Treg cells phenotypes. Inhibition of these reactions may attenuate the expression of inflammatory cytokines in SLE (Linker-Israeli et al.2001, Abou-Raya, Abou-Raya, and Helmii 2013, Ojaimi et al. 2013).

In addition, vitamin D also has an effect on endothelial function because it regulates the production of nitric oxide by endothelial cells, increases the expression of the enzyme nitric oxide synthase, which reduces stiffness of the arteries and oxidation of LDL-c (Molinari et al. 2011, Martinez-Miguel et al. 2014, Andrukhova et al. 2014, Shaul 2003)

SLE patients often present a reduction in serum vitamin D levels, because they are also recommended no exposure to sunlight due to photosensitivity as one of the disease clinical manifestations (Mok 2013).

The study conducted by Aranow et al. 2015 aimed to identify the effects of two different doses of vitamin D_3 supplementation, with a placebo-group, on the IFN signature in stable vitamin D-deficient SLE patients.

The IFN signature (i.e., the overexpression of IFN-inducible genes) was determined based on levels of three IFNα-inducible genes. The authors observed that there was no difference in IFN signature after 12 weeks of intervention. This may be explained due the number of IFN-inducible genes investigated to assess the impact of supplementation, since other studies have included a larger number of genes and only three do not fully represent the IFN signature. Supplementation was also not effective in raising vitamin D_3 to levels greater than 30ng/mL. The group supplemented with the highest dose of vitamin D_3 did not show any symptoms of toxicity,

such as hypercalciuria, but also did not present a decrease in the expression of IFN-α inducing genes, and a reduction in disease activity (Aranow et al. 2015).

The clinical trial conducted by Andreoli et al. 2015 verified the impact of vitamin D_3 intervention on serum vitamin D levels, disease activity, bone health markers and safety parameters of 24-month supplementation, with a cross-over between the groups. The authors suggested that the doses supplemented were safe because they did not alter the calcium-phosphorus metabolism and did not cause calcemia and PTH-suppression, with only mild transient hypercalciuria occurring. Supplementation did not reduce disease activity assessed by SLEDAI, anti-dsDNA levels and levels of C3, C4 and CH50.

The pilot study by Kamen et al. 2015 to determine whether vitamin D_3 repletion improves endothelial function in patients with SLE deficient in this vitamin showed that the subjects with the highest increase in FMD were those who had significantly greater changes in vitamin D levels at the end of the study. The relative difference in FMD between the two groups was clinically important since the 1% change in FMD is associated with a 9% reduction in the risk of cardiovascular events.

The studie by Abou-Raya, Abou-Raya and Helmii 2013 suggested that vitamin D_3 supplementation was effective in decreasing levels of inflammatory and hemostatic markers and disease activity compared to the placebo group, and increase the serum levels of vitamin D substantially to sufficient values.

The study conducted by Terrier et al. 2012 observed that serum vitamin D levels increased significantly without elevation of serum calcium and phosphorus and lithiasis after vitamin D_3 supplementation in patients with hypovitaminosis.

Regarding the interventions performed with vitamin D supplementation, it was observed that doses ranged from 5.000 to 10.000 IU/day. No author used in their study amounts below 800 IU/day for the intervention group. It should be noted, however, that in clinical practice this maximum amount of supplementation allowed to nutritionists (800IU/day) in Brazil has not been shown to be effective in promoting significant changes in insufficient or deficient serum vitamin D levels and in consequent changes in health-related outcomes (Kamen et al. 2015).

Low glycaemic index diet and SLE

Considering that obesity is a frequent situation in SLE patients, whether as a result of disease or corticoid therapy, dietary intervention is also based on this outcome and its subsequent changes such as hyperlipidemia, insulin resistance, sleep quality and fatigue (Davies et al. 2012). The study developed by Davies et al. analyzed the role of a low glycaemic index diet versus a low calorie diet in two groups of women with SLE on the variables cited previously, in addition to identifying variation in body weight and disease activity (Davies et al. 2012).

Studies have suggested that a low-carbohydrate, high-protein and high-fat diet is at least as effective as an energy restriction for weight and cardiovascular disease risk factors reduction (Thomas, Elliot, and Baur 2007, Foster et al. 2010). However, the authors did not observe a significant difference between the two groups in the risk markers of cardiovascular disease at the end of the intervention, probably due to the small number of subjects investigated and the short time intervention. It was not noted improvement in sleep quality and disease activity, but there was improvement of fatigue in both intervention groups, suggesting that manipulation of the diet

associated with weight loss have an important role to play in the management of fatigue in patients with LES.

Turmeric and SLE

Persistent inflammation and tissue damage in SLE may be modulated by the use of antioxidant compounds that suppress the activity of cytokines such as TNF-α and act against reactive oxygen species (ROS) activated by macrophages, monocytes and granulocytes (Aeset, Haugen, and Forre 1998).

Curcumin, a bioactive compound present in turmeric, has been shown to reduce ROS levels in human endothelial cells (Kim et al. 2007). From this, the clinical trial conducted by Khajehdehi et al. identified the effects of turmeric supplementation on proteinuria, hematuria and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis, which is a common manifestation in SLE patients. The results indicated that short-term turmeric supplementation is a beneficial, safe and effective adjuvant therapy for patients because it significantly reduced proteinuria and systolic blood pressure (Khajehdehi et al. 2012).

It should be noted that the process of searching was carried out according all methodological procedures in order to ensure its quality. Nine of eleven studies included in this review obtained a good level of score, above 70%. It reinforces that the studies were methodologically well conducted and their results are relevant for dietary management is SLE patients.

LIMITATIONS

The current revision is not free from limitations, among those is highlighted the difficulty in finding studies that developed intervention, and not only serum analysis of Vitamin D levels or lipid profile. The difficulties reported by the authors were related to the sample size, patients' adherence to the intervention and some studies were not randomized and placebo controlled.

CONCLUSIONS

The studies evidenced that omega-3 supplementation reduced inflammation, disease activity, endothelial dysfunction and oxidative stress; vitamin D supplementation increased their serum levels, reduced inflammatory and hemostatic markers; turmeric supplementation reduced proteinuria, hematuria and systolic blood pressure; and low glycaemic index diet caused weight loss and reduced fatigue.

Other foods and nutrients, such as royal jelly and isoflavones, have been evaluated to improve the symptoms characteristic of SLE, but were only developed in the animal model, which is not the focus of this study. Thus, it is suggested to carry out research in humans with other dietary intervention aimed at improving the different symptoms presented in SLE patients, since the disease presents a broad spectrum of clinical manifestations that could be ameliorated by dietary intervention.

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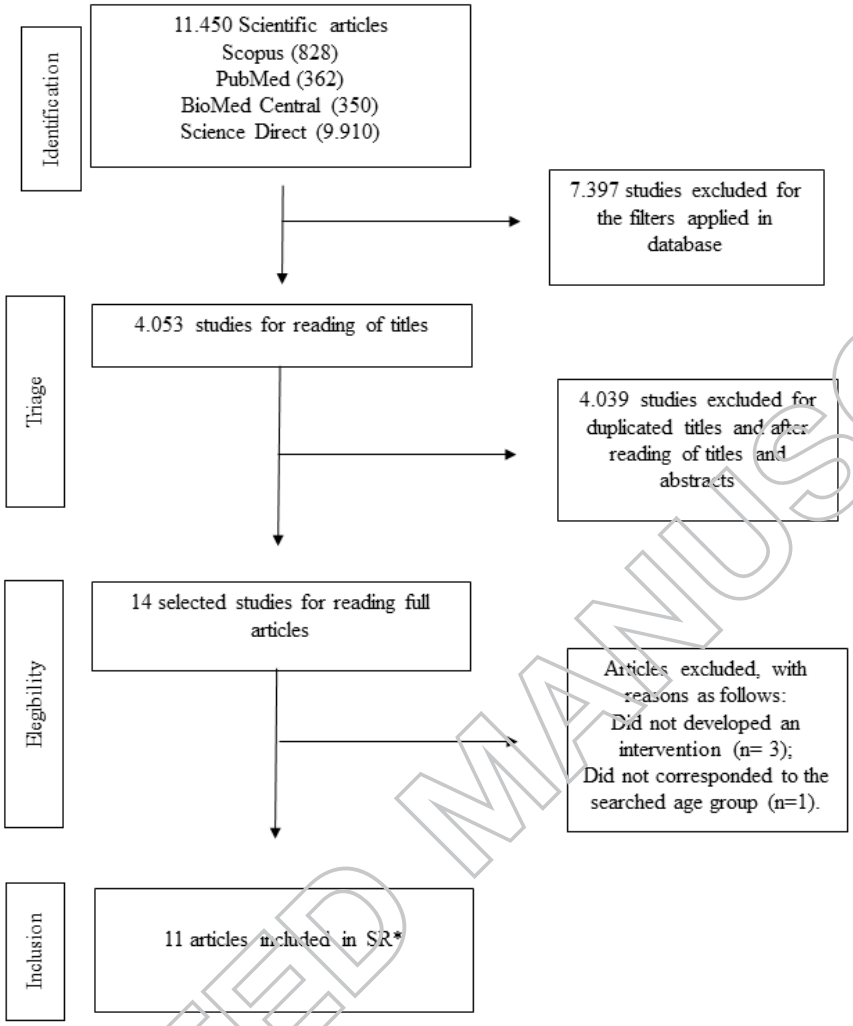

Figure 1. Literature search and selection.

Table 1. Characteristics of included studies.

Study	Country	Sample (gender)	Types of intervention	Duration	Outcomes	Conclusions	Quality scale
Borges et al 2016 (in press)	Brazil	66 women	Omega-3 supplementation 1080mg EPA and 200mg DHA/day No placebo group	12 weeks	Cytokines Adipokines CRP Glucose Lipid profile	Supplementation with omega-3 had no impact on serum concentrations of IL-6, IL-10, leptin and adiponectin in women with SLE and low disease activity. There was a significant	23/32

						decrease of CRP levels as well as evidence that omega-3 may impact total and LDL-cholesterol.	
Aranow et al 2015	United States of America	54 patients	Vitamin D_3 supplementation 4.000 IU/day (high dose group) 2.000 IU/day (low dose group)	12 weeks	IFN signature Disease activity Anti-dsDNA Safety and tolerability	Vitamin D_3 supplementation up to 4.000 IU daily was safe and well-tolerated but failed to diminish the IFN signature in vitamin D–deficient SLE patients. Higher	26/32

						vitamin D levels sustained for a longer duration may be required to affect immunologic outcomes.	
Arriens et al 2015	United States of America	42 women and 8 men	Omega-3 supplementation 2,25g EPA and 2,25g DHA/day (fish oil group) Olive oil refined (placebo	6 months	Quality of life Disease activity	In this randomized, placebo-controlled 6-month trial, SLE patients randomized to fish oil supplementation demonstrated improvement in their PGA,	24/32

			group)			SF-36 and some circulating inflammatory markers.	
Andreoli et al 2015	Italy	34 women	Vitamin D_3 supplementation 300.000 IU at baseline and 50.000 IU/month as maintenance (intensive regimen-IR) 25.000 IU/month (standart regimen-SR)	24 months	Vitamin D levels Disease activity Bone metabolism Anti-dsDNA, C3, C4, CH50 Safety parameters	The IR was safe and effective in obtaining sufficient levels of vitamin D in most SLE patients. However, both regimens of supplementation did not differently affect disease activity nor	22/32

						SLE serology.	
Kamen et al 2015	United States of America	9 women	Vitamin D_3 supplementation 5.000 IU/day (tratament group) 400 IU/day (control group)	16 weeks	Endothelial function Vitamin D levels	These results suggest a potential role for vitamin D in SLE-related endothelial dysfunction and that an adaptive, multi-arm, treat-to-target, serum-level trial design may increase the efficiency and	23/32

						likelihood of success of such a study.	
Bello et al 2013	United States of America	80 women and 5 men	Omega-3 supplementation 1,8g EPA and 1,2g DHA (fish oil group) Starch (placebo group)	12 weeks	Endothelial function Disease activity Inflammatory markers Lipid profile	Omega-3 did not improve endothelial function, disease activity, nor reduce inflammatory markers in SLE. Longer trials might be required if there are delayed clinical effects. There was evidence that omega-3 may increase	26/32

						LDL cholesterol, but not the LDL/HDL ratio.	
Wright et al 2008	Ireland	56 women and 4 men	Omega-3 supplementation 1,8g EPA and 1,2g DHA (fish oil group) Olive oil (placebo group)	24 weeks	Endothelial function Disease activity Oxidative stress	Low-dose dietary supplementation with omega- 3 fish oils in SLE not only has a therapeutic effect on disease activity but also improves endothelial function and reduces oxidative stress and	30/32

						may therefore confer cardiovascular benefits.	
Abou-Raya, Abou-Raya, Helmii 2013	Egipt	228 women and 39 men	Vitamin D_3 supplementation 2.000 IU/day (intervention group) No identified (placebo group)	12 months	Disease activity Proinflammatory cytokines Hemostatic markers	Vitamin D supplementation in patients with SLE is recommended because increased vitamin D levels seem to ameliorate inflammatory and hemostatic markers and show a tendency toward	31/32

						subsequent clinical improvement.	
Terrier et al 2012	France	20 women	Vitamin D_3 supplementation 100.000 IU/week (2 months) 100.000 IU/month (4 months) No placebo group	6 months	Safety T cell and B cell homeostasis Cytokines and gene expresion profiles in peripherol blood mononuclear cells Clinical efficacy assessment	This preliminary study suggests the beneficial role of vitamin D in SLE patients and needs to be confirmed in randomized controlled trials.	20/32
Khajehdehi et al 2012	Iran	22 women and 2 men	Turmeric supplementation	12 weeks	Proteinuria Systolic blood pressure	Short-term turmeric supplementation can	26/32

			1.500mg curcuma 66,3mg curcumina (intervention group) Starch (placebo group)		Serum albumin Hematuria Glomerular filtration rate Blood urea nitrogen	decrease proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis and can be used as an adjuvant safe therapy.	
Davies et al 2012	United States of America	23 women	Dietary intervention 45g/day carbohydrate	6 weeks	Weight loss Tolerability of the diet Biomarkers of	Significant weight loss is achievable over 6 weeks in a diet-	24/32

	10-15% carbohydrate, 25% protein and 60% fat, both saturated and unsaturated fat (low glycaemic index diet group) 2.000kcal/day 50% carbohydrate, 15% protein e 30% fat (low calorie diet group)	cardiovascular risk Fatigue Disease activity Sleep quality	specific trial in subjects with stable SLE, who are on low dose prednisolone. Both diets were equally tolerable, and did not cause flares in disease activity. Our results suggest that dietary manipulation may significantly improve fatigue in subjects with

	SLE.

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; CRP: C-reactive protein; UI: international unit; Physician Global Assessment: PGA.