Relationship of the Inflammatory Diet Status and Dietary Intake with Antimalarial Treatment in Systemic Lupus Rrythematosus: A Cross-Sectional Study

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Research

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Abstract

Background: Systemic lupus erythematosus (SLE) is the prototype autoimmune disease with high inflammatory cytokine levels. In autoimmune conditions, diet could modify the inflammatory status, comorbidities and pharmacotherapy administered in SLE patients. The aim of this study was to assess the relationship of the inflammatory diet status and dietary intake with comorbidities and pharmacotherapy administered in SLE patients.

Methods: A cross-sectional study was conducted in sixty-eight Mexican-Mestizo female SLE patients. Dietary intake was estimated from three 24h food records by Nutritionist Pro-Diet software and 27 food parameters were used to evaluate the inflammatory diet status by the normal dietary inflammatory index (DII®).

Results: SLE patients presented a global pro-inflammatory diet status (DII: 0.71 ± 1.78). Chloroquine (CQ) administration was related to a pro-inflammatory diet status compared to hydroxychloroquine (HCQ) administration, which was related to an anti-inflammatory diet status (CQ= DII score: 1.385±1.327 *vs.* HCQ= DII score: 0.004±2.024; p=0.002). CQ administration conferred a pro-inflammatory DII score (β coefficient= 1.20; CI: 1–2.02; R^2=0.11; p<0.01) and lower total-cholesterol (β coefficient=-29.2; CI: -4.03 to -54.5; R^2=0.07; p<0.05); conversely, HCQ administration conferred an anti-inflammatory DII score (β coefficient= -1.29; CI: -0.46 to -2.12; R^2=0.13; p<0.01). SLE patients with CQ administration had lower intake of energy and 12 nutrients evaluated (CQ *vs.* HCQ; p <0.05), and SLE patients with HCQ treatment had a better achievement ≥100% of daily dietary reference intake (DRI) of energy (HCQ 77% *vs.* CQ 52%; p=0.03), vitamin A (HCQ 65% *vs.* CQ 29%; p<0.01), cholesterol (HCQ 29% *vs.* CQ 3%; p<0.01), and fiber (HCQ 26% *vs.* CQ 6%; p=0.03).

Conclusions: In SLE patients the CQ administration was related to a pro-inflammatory diet status and low total-cholesterol, and HCQ administration with an anti-inflammatory diet status and better dietary intake.

Background

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease characterized by chronic inflammatory processes in several organs and systems. SLE mainly affects women in a 10:1 ratio compared to men [1, 2]. The worldwide prevalence of SLE within autoimmune diseases is low; varies from 3.2-517.5 per 100,000 persons, and in Mexican population the prevalence has been reported in 60 per 100,000 persons [3]. However, despite its low frequency in the general population, SLE is considered the prototype inflammatory autoimmune disease [3].

In SLE has been described a high cardiovascular disease risk mediated by pathogenic mechanisms such as high oxidative stress, high autoantibodies titers and dyslipidemia, that modulate the balance between pro- and anti-inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6 and interferon-gamma (IFN-γ); which are related to increase the tissue damage and systemic clinical manifestations of the SLE [4, 5].

Dyslipidemia in SLE is characterized by low serum levels of high-density lipoprotein cholesterol (HDL-C), and high levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) [6], and a positive energy balance and obesity are factors that modulate its clinical manifestations [7]. Additionally, corticosteroid pharmacotherapy used in SLE contributes to dyslipidemia development, and high administration

of prednisone can stimulate lipolysis, and high fatty acids serum levels [8]. On the other hand, antimalarial drugs administration such as hydroxychloroquine (HCQ) and chloroquine (CQ) have been associated with reduction of dyslipidemia frequency in SLE patients [5, 9]. However, its prolonged administration could develop side effects such as taste disorders in flavors perception like dysgeusia, which may modify eating behavior, appetite and healthy food selection [10].

Furthermore, diet highlights as a key factor that could modify inflammatory mediators and lipids serum levels, because several nutrients such as vitamins have been related to play a fundamental role in the inflammatory processes modulation [10, 11]. A moderate intake of calories and nutrients, physical activity and reduction in body fat, contribute to decrease inflammatory activity and comorbidities in SLE [12]. In contrast, an excessive intake of calories, proteins, simple carbohydrates, saturated and *trans* fats, have been linked with dyslipidemia, high levels of acute-phase reactants, and inflammatory cytokines such as TNF-α in SLE [12, 13].

In the general population, unhealthy dietary patterns such as Western diet have been associated with high inflammatory mediators levels, while healthy dietary patterns such as Mediterranean diet, are related to an anti-inflammatory status [14, 15]. Nevertheless, these qualitative characteristics of the anti or pro-inflammatory properties of foods in each diet, had not been quantified by dietary inflammatory scores in several studies [14].

Recently, the dietary inflammatory index (DII®) has been proposed as a dietary standardized tool to assess the inflammatory potential of diet in a quantitative way [14]. The DII is based on evaluation of 45 dietary parameters associated to an increase or decrease of 6 inflammatory biomarkers (CRP, IL-6, TNF-, IL-1β, IL-4 and IL-10). A positive DII score is related to a pro-inflammatory diet status, and conversely, negative scores are related to an anti-inflammatory diet status [14–20]. Therefore, the DII could be of potential use in autoimmune pathologies such as SLE, where the inflammatory component is high and is influenced by diet.

In SLE Mexican-Mestizo population, a high prevalence of excess weight (70%) have been associated with high clinical activity, and the common features observed in SLE patients are the presence of dyslipidemia, deficiencies in micronutrient intake and high frequency (> 50%) of corticosteroid pharmacotherapy administered [7]. Nonetheless, the inflammatory status of diet consumed by the SLE patients and the potential relationship with the main comorbidities in SLE such as dyslipidemia and obesity, as well as the pharmacotherapy administered is unknown. Therefore, based on these previous findings, our aim was to assess the relationship of the inflammatory diet status and dietary intake with comorbidities and pharmacotherapy administered in SLE patients.

Methods

Subjects

A cross-sectional study was conducted in 68 female SLE patients from an unrelated Mexican-Mestizo population, classified according to the 1997 SLE American College of Rheumatology (ACR) criteria [21], recruited as volunteers, between 2017 and 2019 from the Rheumatology Department of the *Hospital Civil Fray Antonio Alcalde*, Guadalajara, Jalisco, Mexico.

The disease remission/activity presented at enrollment in the study was evaluated by the Mexican-Systemic Lupus Erythematosus-Disease Activity Index (Mex-SLEDAI) [21], and the chronicity was evaluated by the

Systemic Lupus International Collaborating Clinics (SLICC) criteria [22]. All SLE patients included in the study, presented no recent infections, trauma nor surgery, pregnancy, neither other autoimmune conditions not related to SLE.

Ethical Considerations

All SLE patients before enrollment to the study provided signed written informed consent, and the study was approved by the Research Ethical Committee of the University of Guadalajara (CI-05018 CUCS-UdeG), based on national and international ethical guidelines.

Anthropometric Measurements

Body composition and weight were determined in the morning through bioimpedance analysis prediction method (TANITA® Ironman™ body composition Monitor BC-549, Arlington Heights, IL, USA), height was measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Waist and hip circumferences were measured twice using a flexible metal tape with an accuracy of ± 0.1 cm (Lufkin® executive thinline W606ME, USA), with subject standing with feet together and arms crossed. Waist circumference was measured at midpoint between the costal margin and iliac crest in the mid-axillary line in standing position at the end of a gentle expiration. The hip circumference measurement was taken around the widest portion of the buttocks [23].

Biochemical Measurements

Glucose, high sensitivity CRP (hs-CRP), albumin, and lipid profile: TC, TG, HDL-C, and LDL-C levels were quantified from blood serum samples (overnight fast 12 h) using semi-automated equipment (Mindray-BS-240 Clinical Chemistry Analyzer, Shenzhen, China) with colorimetric enzymatic assays with BioSystem® kits (Barcelona, Spain).

TNF-α serum levels quantification

TNF-α serum levels determination was performed by a commercial ELISA kit (KHC3011; Invitrogen™, Thermo Fisher Scientific, Inc., USA) according to the manufacturer's instructions. The TNF-α assay sensitivity was 1.7 pg/mL.

Nutritional Assessment

Evaluation of food consumption was made in a personal interview carried out by a trained nutritionist-dietician by collecting three 24 h food records (two weekdays and one weekend day), based on the validated questionnaires proposed by the 2016 Mexican National Health and Nutrition Survey (ENSANUT by its Spanish acronym) [24]. For a more accurate quantitative estimation of the food intake in SLE patients, they were asked for quantity, type or variety, and the additives used in the preparation of the meals, with the support of the "Mexican food photograph album" validated for the visual estimation of food in the Mexican population [25].

Energy, nutritional requirements and dietary references intakes

Energy and nutritional content calculation of the collected dietary records was performed with Nutritionist Pro Diet software (Axxya Systems, Washington, DC, USA). For each patient, energy requirement was calculated

according to their individual total energy expenditure: BMR + 10% of the thermic effect of food + 10% of physical activity (sedentary) [26].

Adequate consumption of macronutrients requirement was calculated using the average of the Mexican recommended distribution range ((min + max)/2) as a cut-off point: carbohydrates (59%), added sugars (<10%), proteins (17.5%), total fat (27.5%), saturated fat (<7%), monounsaturated fat (<15%), polyunsaturated fat (8%), trans fat (<1%), omega 6 (6.5%) and omega 3 (1.5%) [26], and values of daily average of others nutrients intake were based on the following dietary reference intake (DRI): a) recommended dietary allowance (RDA) and b) adequate intake (AI) of the NOM-051-SCFI/SSA1-2010-MEX (modification 2020) [27], and based on the recommendations of the food and agriculture organization (FAO), depending to the nutrient evaluated [28].

Inflammatory diet status assessment

Inflammatory diet status was assessed calculating the normal DII® version. The normal DII is a dietary standardized tool based on a global database which includes 45 DII food parameters from 11 populations around the world [14]. In the normal DII calculation of diet from SLE patients, we included 27 of the 45 food parameters of the normal DII: energy, dietary fiber, carbohydrates, proteins, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, *trans* fat, cholesterol, omega 3 and omega 6 fatty acids, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, thiamin, riboflavin, niacin, vitamin B6, folic acid, vitamin B12, and β-carotene.

Individual intake of each food parameter were standardized to global intakes taken as DRI, using means and standard deviations for each parameter derived from 11 populations around the world, which one of them is Mexico, with data obtained from the 2006 ENSANUT data [14,29].

Following the DII calculation, standardized scores of intakes (Z-scores) were converted to proportions and were centered. These centered proportions of specific food intake were multiplied by their inflammatory effect score and summed to formulate the overall DII score of an individual's diet, according to the normal DII calculation explained in detail in previous studies [18]. Positive scores indicate more pro-inflammatory diet status, and negative scores indicate more anti-inflammatory diet status [13–15].

Statistical Analysis

Statistical analyses were performed by the STATA v 9.2 (College Station, TX, USA) and GraphPad Prism v 5.0 (San Diego, CA, USA) software. For descriptive analysis, nominal variables were expressed as frequencies; Gaussian distribution was determined by Shapiro-Wilk test and based on this, continuous variables with parametric distribution were expressed as means ± standard deviation (SD) and nonparametric variables as medians and percentiles 5^{th}–95^{th}.

For inferential analysis, χ^2 test was used to compare proportions. For parametric quantitative determinations Student's T-test or Anova One-Way test were used, and for nonparametric quantitative determinations Mann–Whitney U test or Kruskal-Wallis test were applied.

DII scores were also analyzed by tertiles (T) stratification, from the most anti-inflammatory to the most pro-inflammatory scores: $T1^{st}$ (anti-inflammatory score: minimum value at <0.008), $T2^{nd}$ (medium pro-inflammatory

score: ≥0.008 to <1.7), T3rd (high pro-inflammatory score: ≥1.71 to maximum value).

According to the antimalarial treatment, we also evaluated stratifying by CQ and HCQ administration: a) DII scores, b) nutrient intake, and c) SLE patients frequency that achieve their energy and nutrient DRI by RDA or AI cutoff of each nutrient consumed, taking as a reference the achievement of ≥100% of the DRI of each nutrient evaluated.

To assess the effect of CQ and HCQ administration on the DII score, and lipid profile levels, we used models of linear regression. All differences were considered significant with *p* value < 0.05.

Results

General and clinical characteristics of SLE patients

Sixty-eight female SLE patients were evaluated with a median age of 33.5 (20–59) years old, and a disease evolution time of 5.75 (1–21) years. The patients presented remission of the disease activity, with a Mex-SLEDAI index median score of 0 (0-8) and the drugs administered with highest prescription were antimalarial drugs such as CQ (44.1%) and HCQ (45.6%) (Table 1).

SLE patients showed an optimal median blood pressure of 111/75 mmHg. Concerning hs-CRP levels, we observed a median value of 2.6 mg/L, considered as average cardiovascular disease risk (1.0 to 3.0 mg/L) [30], and TNF-α serum levels were high (18.9 pg/mL). Regarding biochemical variables, they had values within the normal reference range [27,28], with median values of 85.3 mg/dL of glucose, 102 mg/dL of TG, 163 mg/dL of TC, 43.9 mg/dL of HDL-C and 93.4 mg/dL of LDL-C and an atherogenic index score (TC/HDL-C) classified as low risk (score: 3.67) [31] (Table 1).

General and clinical characteristics stratified by the DII

Regarding the DII score of total SLE patients, we observed a mean of 0.71 ± 1.78, which is considered characteristic of a pro-inflammatory diet status (Table 1). When we evaluated these variables according to the DII stratified in tertiles (T) from the anti-inflammatory DII score (T1st) to the most pro-inflammatory DII score (T3rd), we did not find significant differences in the comparison of biochemical and clinical variables related to SLE comorbidities according to the DII tertiles stratification, but we observed a trend in the T3rd of a higher distribution of the Mex-SLEDAI scores from 0 to 8, and higher hs-CRP serum levels with a median of 3.39 mg/L classified as high cardiovascular risk (>3 mg/L) in comparison to the T1st (2.43 mg/L), and the T2nd DII tertiles (2.6 mg/L), which were in the lower cardiovascular risk by hs-CRP, without significant differences.

Regarding TNF-α serum levels, we observed a trend in the T2nd DII tertile, which showed higher TNF-α values (22.8 pg/mL). About the lipid profile, we observed a trend in the T3rd of lower serum HDL-C (42.9 mg/dL) as well as a higher atherogenic index score of 3.89, compared to the other tertiles 1st and 2nd (Table 1).

Anthropometric characteristics of SLE patients and DII

The SLE patients evaluated had an average height of 159 cm and a bodyweight of 66.9 kg. When we assessed the BMI, 33.8% presented overweight, and 20.6% obesity. Comparing by the DII tertiles, SLE patients in the T3rd DII

tertile showed a trend with no significant differences of a higher frequency of overweight (50%) and obesity (22.7%) according to BMI. Also, they present a tendency to higher BMI score (26.9 kg/m^2), body fat percentage (34.6%), metabolic age (47 years old), arm circumference (30.7 cm) and waist circumference (86.8 cm) in comparison with those SLE patients located in the 1st and 2nd tertiles (Data no shown).

Nutrient intake in SLE patients and DII

We observed according to the DII tertiles that SLE patients of the most pro-inflammatory T3rd DII tertile, had a significant lower consumption of 20/27 food parameters included in this DII calculation (p <0.05). These 20 nutrients presented a significant negative correlation (p <0.01) with the total DII, of which the majority present an anti-inflammatory effect such as: fiber (15.9 g/day; r=-0.83), vitamin B6 (0.98 mg/day; r=-0.83), folic acid (190 µg/day; r=-0.72), and magnesium (211 mg/day; r=-0.73); as well as some with pro-inflammatory effect such as: energy (1308 calories; r=-0.55), proteins (50.4 g/day; r=-0.58), cholesterol (131 mg/day; r=-0.34), and iron (8.20 mg/day; r=-0.74) (Data no shown).

Inflammatory diet status according to antimalarial treatment

Notably, we observed a significantly higher frequency of CQ administration in SLE patients located in the pro-inflammatory T3rd tertile (59 %; p= 0.04) with a low dose of administration of this drug (T3rd=153 ± 43.11 mg/day; p =0.04), in comparison with SLE patients located in the others tertiles (Table 1).

Concerning to SLE patients with CQ treatment observed in the T1st tertile, they presented higher administration dose of this drug (T1st = 160 mg/day *vs.* T2nd and T3rd = <160 mg/day; p =0.04) (Table 1). For HCQ, we found a higher frequency of its administration in the anti-inflammatory DII tertile 1st (T1st= 73%, p= 0.01), with no differences between doses treatment (200 mg/day in all tertiles) (Table 1).

According to these results, we observed that SLE patients with CQ administration presented a pro-inflammatory diet status compared to SLE patients with HCQ administration, who presented an anti-inflammatory diet status (CQ= DII score: 1.385±1.327 *vs.* HCQ= DII score: 0.004±2.024; p=0.002) (Figure 1).

Also, we also observed that CQ administration conferred significant positive score of 1.20 points in the DII score, which is related to a pro-inflammatory diet status (β coefficient= 1.20; CI: 1–2.02; R^2=0.11; p<0.01), and significant lower values of total-cholesterol serum levels (β coefficient=-29.2; CI: -4.03 to -54.5; R^2=0.07; p<0.05), in comparison with SLE patients with no CQ administration (Data no shown).

Regarding HCQ administration, this conferred a significant negative score of - 1.29 points in the DII score, which is related to an anti-inflammatory diet status (β coefficient= -1.29; CI: -0.46 to -2.12; R^2=0.13; p<0.01) (Data no shown).

Nutrient intake in SLE patients with antimalarial pharmacotherapy

Regarding to our findings of a pro-inflammatory diet status in SLE patients with CQ administration and an anti-inflammatory diet status in SLE patients with HCQ administration, we decided to compare their nutrient intakes between this two subgroups. SLE patients with CQ administration had a significantly lower intake of energy (CQ: 1372 kcal *vs.* HCQ:1556 kcal; p <0.05), fiber (CQ: 19.5 g *vs.* HCQ: 23.9 g; p=0.02), saturated fat (CQ: 12.2 g *vs.*

HCQ: 18.1 g; *p*=0.02), cholesterol (CQ: 132 mg *vs.* HCQ 193 mg; *p*=0.03) as well as vitamins with anti-inflammatory properties such as vitamin A (CQ: 23 RE *vs.* HCQ: 789 RE; *p*<0.001), vitamin D (CQ: 2.52 µg *vs.* HCQ: 4.13 µg; *p*<0.01), thiamin (CQ: 1.02 mg *vs.* HCQ: 1.25 mg; *p*=0.01), riboflavin (CQ: 1.08 mg *vs.* HCQ: 1.22 mg; *p*=0.03), folic acid (CQ: 218 µg *vs.* HCQ: 248 µg; *p*=0.01), vitamin E (CQ: 0.59 mg *vs.* HCQ: 1.33 mg; *p*<0.01), β-carotene (CQ: 933 µg *vs.* HCQ: 2345 µg; *p*=0.001), and some minerals such as iron (CQ: 9.35 mg *vs.* HCQ: 11.2 mg; *p*=0.02), and magnesium (CQ: 253 mg *vs.* HCQ: 310 mg; *p*=0.01), in comparison to SLE patients with HCQ treatment (Table 2).

When we evaluate the frequency of SLE patients who achieved the 100% of daily DRI of each nutrient assessed depending to the CQ or HCQ administration, we observe significant differences of the achievement of the DRI in SLE patients with HCQ administration in the following nutrients: energy (DRI: ≥1358 kcal; HCQ: 77% *vs.* CQ: 52%; *p*=0.03), vitamin A (AI: 568 RE; HCQ: 65% *vs.* CQ: 29%; *p*<0.01), cholesterol (DRI: <300 mg; HCQ: 29% *vs.* CQ: 3%; *p*<0.01) and fiber (RDA: 30 g; HCQ: 26% *vs.* CQ: 6%; *p*=0.03), in comparison to SLE patients with CQ treatment (Figure 2).

Regarding other nutrients evaluated, we not observed significant differences in this comparison between CQ *vs.* HCQ pharmacotherapy, but a similar pattern with a trend of high achievement ≥ 100% of daily DRI in SLE patients with HCQ administration was observed in the following nutrients: riboflavin (AI: ≥0.84 mg; HCQ: 90% *vs.* CQ: 77%; *p* >0.05), saturated fat (DRI: ≥11.9 g; HCQ: 84% *vs.* CQ: 81%; *p* >0.05), thiamin (AI: ≥0.8 mg; HCQ: 87% *vs.* CQ: 71%; *p* >0.05), magnesium (AI: ≥248 mg; HCQ: 81% *vs.* CQ: 58%; *p* >0.05), β-carotene (DRI: ≥3718 µg; HCQ: 29% *vs.* CQ: 13%; *p* >0.05), folic acid (AI: ≥380 µg; HCQ: 13% *vs.* CQ: 3%; *p* >0.05), iron (AI: ≥17 mg; HCQ: 11% *vs.* CQ: 0%; *p* >0.05) and vitamin D (AI: ≥10 µg; HCQ: 6% *vs.* CQ: 3%; *p* >0.05), in comparison to SLE with CQ administration (Figure 2).

Discussion

In SLE patients a high frequency of atherogenic dyslipidemia related to cardiovascular risk disease have been described [6, 32, 33]. A longer disease evolution time, higher corticosteroids cumulative dose, and absence of antimalarial therapy have been described as predictor factors of cardiovascular disease in SLE [32].

However, in our study, SLE patients presented normal serum levels of lipid profile, with lower levels of TG, TC, and LDL-C compared with other studies performed in SLE patients [6, 33, 34]. Serum HDL-C levels in the present study were found within the normal range with higher values compared to other studies [6, 33].

The differences in the dyslipidemia frequency in our study in comparison to other studies could be explained in part by the low clinical activity disease and the high antimalarial pharmacological treatment observed. A high frequency of SLE patients evaluated in the present study, were in clinical activity remission (63%), in comparison to other studies in SLE patients from other countries, where the general prevalence of SLE patients with clinical activity has been described higher [6, 33, 35].

In several studies, SLE patients with dyslipidemia had a higher frequency of glucocorticoid administration, around of 70% [6, 35], while in the present study, it was only 31%. In contrast, the antimalarial pharmacotherapy was higher in our study, reaching almost 90% of SLE patients, considering CQ and HCQ administration, while in other studies the combined frequency has been described less than 64% [34, 35].

The CQ and HCQ use is effective in the treatment of SLE [36], it has been reported that SLE patients with this pharmacotherapy have a beneficial effect against the occurrence of diabetes, thrombotic events, and dyslipidemia, especially those treated with HCQ [37]. Two prospective studies found significantly lower levels of LDL-C, VLDL, and triglycerides as well as higher HDL-C concentrations in SLE patients treated with HCQ [4, 37]. The antimalarial drugs promote the LDL-C receptors upregulation with an enhancement of the plasma removal of this lipoprotein; besides, an overall reduction in hepatic cholesterol synthesis by the accumulation of LDL-C in the lysosome and to block cholesterol transport out of this organelle have been described [4, 37–39].

The lipid-lowering effects of the antimalarial drugs were also observed in the present study, the CQ administration conferred significant lower TC serum levels. Nevertheless, this same pattern was no observed in SLE patients with HCQ treatment.

Notably, we found that CQ administration was associated with a pro-inflammatory diet status evaluated by the DII score. We hypothesized that this finding may be influenced by the secondary effect reported about of antimalarial treatment; in particular in the CQ administration [40]. Approximately 20% of the patients treated with CQ had reported anorexia, abdominal pain, heartburn, nausea, vomiting, or diarrhea [41], which could influence the appetite and indirectly their food choices, for foods with a higher caloric density and simple sugar content.

Other gastrointestinal adverse effects that may occur with the CQ treatment are loss of taste functions of the tongue, such as ageusia [42]. In a previous study conducted in patients with malaria, the CQ administration improved the symptoms of headache, fever, and chills, but it increases the frequency of nausea (46%), diarrhea (26%), abdominal pain (38%) and bitter taste in the mouth (60%) [43], which could be related to the high doses administered in patients with this pathology.

The relationship between a higher frequency of CQ administration with a more pro-inflammatory DII score observed in our study, could be influenced by the residual accumulation of antimalarials drugs in different organs and tissues [10, 41]. The antimalarials could modulate the taste functions because they may stimulate interactions between the innate immune response and the taste signal transmission in the taste bud cells [10]. Taste bud cells have several signaling molecules associated with the innate immune response; express pathogen-associated molecular patterns (PAMPs) recognition receptors, such as Toll-like receptors (TLRs) and their adaptor proteins, as cytokines and chemokines [10, 44]. Whereby, these TLRs have an emerging role in the subsequent regulation of taste bud functions [10]. Alterations in these signaling pathways could influence the food choices, decrease the appetite and contribute to have a lower consumption of their energy and nutrient requirements in patients with gastrointestinal adverse effects related with the CQ administration, and this would be reflected in higher pro-inflammatory DII scores.

The CQ gastrointestinal side effects may be controlled by reducing drug dose administered [43]. Conversely, in the present study, SLE patients located in the most anti-inflammatory DII tertile (T1st) had a higher CQ daily dose in comparison with SLE patients with the same antimalarial treatment located in the most pro-inflammatory DII scores (T3rd), who had a higher frequency of CQ administration but in a lower dose, which could indicate that CQ may have a dose-dependent effect in the pro or anti-inflammatory diet status evaluated by the DII.

Patients with HCQ administration presented an anti-inflammatory diet status related to a negative DII score. One explanation to this finding could be the safety profile in the HCQ administration reported in other studies conducted in SLE patients [40, 41], because its administration has been related to lower frequency of adverse

effects (< 10%), in comparison with CQ administration [40, 41], and only HCQ may cause a temporal and reversible ageusia [42], which could be reflected in greater availability of nutrients for the patients with this pharmacotherapy.

In several studies, a pro-inflammatory diet status has been related to high fats diets, simple carbohydrates, cholesterol, and saturated fats consumption [18, 45]. In contrast, an anti-inflammatory diet status has been characterized by an adequate content of nutrients such as omega 3 fatty acids, fiber, several, and minerals associated with decrease the levels of inflammation mediators [45]. In our study was observed a pattern that while the DII was higher, the nutrient intake was lower, because the patients in the most pro-inflammatory DII tertile (T3rd) had considerably lower consumption of 20/27 dietary parameters evaluated in the DII, compared with the SLE patients with lower DII scores.

When we evaluated the differences in the dietary intake of SLE patients with antimalarial pharmacotherapy, we observed that SLE patients with CQ treatment had lower consumption of nutrients evaluated in comparison to SLE patients with HCQ treatment. Highlighting those SLE patients with HCQ treatment had a better achievement of the 100% of daily DRI in the following nutrients: energy, cholesterol, vitamin A, fiber, riboflavin, saturated fat, thiamin, magnesium, β-carotene, folic acid, iron and vitamin D.

Regarding this, there are no studies in the literature evaluating the relationship of antimalarial pharmacotherapy with nutritional status and nutrient intake, which will be necessary in order to make an appropriate comparison with other SLE populations with a similar antimalarial treatment. Nevertheless, several studies have linked the presence of nutritional deficits with immune pro-inflammatory imbalances [12], SLE patients in the present study were deficient in the intake of the nutrients evaluated and few patients reached the daily DRI for these nutrients, which is indicative of a poor nutritional adequacy of the diet consumed by these patients.

Therefore, a correct nutritional adequacy is essential to ensure the adequate dietary intake of nutrients described with an anti-inflammatory effect in patients with autoimmune diseases, such as immune-modulatory vitamins like vitamins A, C, D and E, minerals such as magnesium, and zinc, as well as β-carotenes and polyunsaturated fats such as omega 3, because their intakes are characterized by contributing to the decrease of the levels of IL-1β, IL-6, TNF-α and CRP, and increasing the levels of inmunomodulatory cytokines such as IL-4 and IL-10, which could influence to obtaining a general anti-inflammatory status [45].

Although we observed in SLE patients the relationship of CQ administration with a pro-inflammatory diet status, and HCQ administration with an anti-inflammatory diet status; these results should be interpreted with caution. The limitations of our study were that we were not able to assess the gastrointestinal symptoms related with CQ and HCQ administration in a dose-dependent manner, which could clarify part of the findings found, in order to make a complete comparison between SLE patients subgroups with antimalarial pharmacotherapy. Moreover, the consumption deficiencies found in SLE patients with CQ treatment may not be represented in their blood serum levels, because the dietary records are subject to memory errors, and may not represent fully the routine intake of the patients evaluated.

Statistically, our cross-sectional study design limits us by simply showing a relationship between antimalarial treatment and inflammatory diet status, but we do not suggest causality. Nonetheless, the present study provides evidence of the potential relationship of antimalarial pharmacotherapy with nutritional deficiencies related to a pro-inflammatory status of diet consumed by SLE patients.

Therefore, further prospective studies in a SLE Mexican population cohort will be necessary to perform, in order to evaluate causality in the relationship between antimalarial pharmacotherapy and dietary inflammatory status described in this cross-sectional study. This will help to support the nutritional interventions in subsequent studies conducted in autoimmune patients with antimalarial pharmacotherapy.

Conclusions

In SLE patients the CQ administration was related to a pro-inflammatory diet status and lower TC; conversely, the HCQ treatment was related to an anti-inflammatory diet status and better dietary intake; which could suggest that antimalarial treatments have a different relationship with diet consumed and lipid profile in SLE patients.

Abbreviations

ACR
American College of Rheumatology
AI
adequate intake
BMI
body mass index
CQ
chloroquine
DII
dietary inflammatory index
DRI
dietary reference intake
ENSANUT
Mexican National Health and Nutrition Survey
HCQ
hydroxychloroquine
HDL-C
high-density lipoprotein cholesterol
hs-CRP
high sensitivity C-reactive protein
Kcal
kilocalories
IL-1β
interleukin 1 beta
IFN-γ
interferon-gamma
LDL-C
low-density lipoprotein cholesterol
Mex-SLEDAI
Mexican-Systemic Lupus Erythematosus-Disease Activity Index

µg
micrograms
mg
miligrams
NOM
Mexican official dietary standard
RDA
recommended dietary allowance
RE
retinol equivalents
SLE
systemic lupus erythematosus
SLICC
Systemic Lupus International Collaborating Clinics
TG
triglyceride
TNF-α
tumor necrosis factor-alpha
TC
total-cholesterol

Declarations

Ethics approval and consent to participate

All SLE patients before enrollment to the study provided signed written informed consent, and the study was approved by the Research Ethical Committee of the University of Guadalajara (CI-05018 CUCS-UdeG), based on national and international ethical guidelines.

Consent for publication

Not applicable

Availability of data and materials

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

James R. Hébert owns a controlling interest in Connecting Health Innovations LLC (CHI). This company has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counselling and dietary intervention in clinical settings. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

The other authors declare that they have no competing interests.

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Authors' contributions: Ulises De la Cruz-Mosso: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Project administration and Funding acquisition. Monica R. Meza-Meza: Writing- Original draft preparation, Formal analysis, Investigation and Writing - Review & Editing. Nitin Shivappa: Methodology, software, Formal analysis and Writing - Review & Editing. Margarita Montoya-Buelna: Methodology, Formal analysis and Writing - Review & Editing. José Francisco Muñoz-Valle: Methodology, Formal analysis and Writing - Review & Editing. James R. Hébert: Methodology, software, Formal analysis and Writing - Review & Editing. Barbara Vizmanos-Lamotte: Methodology, Formal analysis and Writing - Review & Editing. Isela Parra-Rojas: Methodology, Formal analysis and Writing - Review & Editing. Bertha Campos-López: Formal analysis, Investigation and Writing - Review & Editing. Sergio Cerpa-Cruz: Formal analysis, Investigation and Writing - Review & Editing. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors read and approved the final manuscript.

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Tables

Table 1. Clinical and biochemical characteristics of SLE patients stratified according to the DII tertiles

Variable	Total (n=68)	Dietary Inflammatory Index (DII) tertiles			
		T1st (n=22)	T2nd (n=24)	T3rd (n=22)	*p* value
Age (years)[a]	33.5 (20–59)	33.5 (19–56)	35 (20–58)	32 (21–66)	0.9
Disease evolution (years)[a]	5.75 (1–21)	3 (0.5–20)	7.5 (2–21)	9 (1–23)	0.1
SLICC-DI score[a]	0 (0–4)	0 (0–4)	0 (0–4)	0 (0–4)	0.4
Mex-SLEDAI score[a]	0 (0–8)	0 (0–7)	0 (0–7)	0 (0–8)	0.7
Antibodies (positive)					
ANAS (%)[b]	96 (45/47)	94 (17/18)	100 (14/14)	93 (14/15)	0.6
Anti-dsDNA (%)[b]	71 (25/35)	82 (9/11)	64 (9/14)	70 (7/10)	0.6
Treatment					
Prednisone (%)[b]	31 (21/68)	36 (8/22)	25 (6/24)	32 (7/22)	0.7
Chloroquine (%)[b]	44 (30/68)	23 (5/22)	50 (12/24)	59 (13/22)	**0.04**
Chloroquine dosis (mg/day)[c]	156 ±34.07	160 ±41.83	158 ±19.46	153 ±43.11	**0.04**
Hydroxychloroquine (%)[b]	46 (31/68)	73 (16/22)	29 (7/24)	36 (8/22)	**0.01**
Hydroxychloroquine dosis (mg/day)[a]	200 (200-200)	200 (200-200)	200 (200-200)	200 (150–200)	0.2
Azathioprine (%)[b]	32 (22/68)	18 (4/22)	33 (8/24)	45 (10/22)	0.1
Mycophenolic acid (%)[b]	26 (18/68)	27 (6/22)	37 (9/24)	14 (3/22)	0.2
NSAID (%)s[b]	28 (18/65)	33 (7/21)	22 (5/23)	28 (6/21)	0.7
SBP (mmHg)[a]	111 (97–140)	110 (97–140)	115 (100–138)	110 (90–140)	0.8
DBP (mmHg)[a]	75 (60–90)	72 (60–90)	77 (64–89)	74 (60–91)	0.3
hs-CRP (mg/L)[a]	2.6 (0.6–19.1)	2.43 (0.21–36)	2.6 (0.8–15.9)	3.39 (0.15–28.5)	0.4
TNF-α (pg/mL) [a]	18.9 (7.82–35.6)	16.9 (7.82–33.3)	22.8 (7.49–36.1)	17.2 (8.48–35.6)	0.7
Biochemical parameters					
Glucose (mg/dL)[a]	85.3 (72.9–106)	86.8 (73.9–105)	84.6 (76.1–106)	85.6 (65–112)	0.9
Albumin (g/dL)[a]	4.06 (3.02–4.6)	4.00 (2.63–4.5)	4.00 (3.44–4.51)	4.24 (3.49–4.67)	0.4

Lipid profile					
Triglycerides (mg/dL)[a]	102 (46.7–245)	106 (48.9–296)	110 (45.1–196)	99.5 (49.7–180)	0.6
Total-cholesterol (mg/dL)[a]	163 (110–251)	168 (115–313)	162 (110–259)	158 (113–224)	0.8
HDL-C (mg(dL)[a]	43.9 (25.5–66.6)	45.9 (31.3–62.4)	47.4 (23.8–66.6)	42.9 (30.6–67.0)	0.7
LDL-C (mg/dL)[a]	93.4 (53.7–156)	96.2 (60.8–197)	89.1 (55.3–158)	93.9 (53.7–141)	0.9
Atherogenic index score (TC/HDL-C) [a]	3.67 (2.28–6.4)	3.62 (2.83–5.84)	3.6 (2.35–6.4)	3.89 (2.2–6.04)	0.9
DII score[c]	0.71 ± 1.78	-1.32 ± 1.12	0.82 ± 0.49	2.62 ± 0.69	-

[a]Data provided in median ($p05^{th}$–$p95^{th}$), Kruskal-Wallis test. [b]Data provided in percentages, χ^2 test. [c]Data provided in mean ± standard deviation, ANOVA test. **SLICC:** systemic lupus international collaborating clinics. **Mex-SLEDAI:** Mexican systemic lupus erythematosus disease activity index. **ANAs:** antinuclear antibodies. **dsDNA:** double stranded DNA. **NSAIDs:** non-steroidal anti-inflammatory drugs. **SBP:** systolic blood pressure. **DBP:** diastolic blood pressure. **mmHg:** millimeters of mercury. **DII:** dietary inflammatory index. **hs-CRP:** high sensitivity C-reactive protein. **TNF-α:** tumor necrosis factor-alpha. **LDL-C:** low-density cholesterol. **HDL-C:** high-density cholesterol. **TC:** total cholesterol. **mg:** milligrams. **pg:** picograms. **L:** liter. **mL:** milliliter. **dL:** deciliter. Bold numbers indicate statistical significance (p <0.05).

Table 2. Energy and dietary intake stratified according to the antimalarial administration in SLE patients

Variable	Chloroquine (CQ) (n=31)	Hydroxychloroquine (HCQ) (n=31)	DRI	*p* value
Energy (calories)[a]	1372 (1043 - 2026)	1556 (1024 - 2366)	1563 (1358 -1962)	**<0.05**
Fiber (g)[b]	19.5 (8.75 - 42.4)	23.9 (11.2 - 37.4)	30**	**0.02**
Macronutrients				
Carbohydrates (g)[a]	194 ± 57.6	213 ± 55.8	230 (200 - 289)	0.2
Proteins (g)[b]	61.7 (31.7 - 103)	69.9 (38.1 - 107)	68.4 (59.4 - 85.8)	0.1
Total fat (g)[b]	42.8 (27.2 - 78.2)	55.9 (29.1 - 115)	47.7 (41.5 - 59.9)	0.1
Saturated fat (g)[b]	12.2 (6.39 - 25.2)	18.1 (8.47 - 30.7)	11.9 (10.4 - 15.0)	**0.02**
Monounsaturated fat (g)[b]	13.5 (8.44 - 24.7)	16.2 (7.28 - 31.6)	25.8 (22.4 - 32.4)	0.2
Polyunsaturated fat (g)[b]	8.79 (4.91 - 18.8)	10.4 (4.43 - 24.3)	13.8 (12.1 - 17.4)	0.5
Trans fat (g)[b]	0.32 (0.01 - 1.64)	0.51 (0.08 - 1.75)	1.72 (1.49 - 2.16)	0.1
Omega 3 fatty acids (g)[b]	0.52 (0.32 - 1.10)	0.58 (0.34- 5.87)	2.60 (2.26 - 3.27)	0.3
Omega 6 fatty acids (g)[b]	6.84 (4.18 - 17.6)	7.77 (3.89 - 15.9)	11.3 (9.81 - 14.2)	0.7
Cholesterol (mg)[b]	132 (61.8 - 277)	193 (58.5 - 423)	<300***	**0.03**
Vitamins				
Vitamin A (RE)[b]	323 (57.5 - 1510)	789 (238 - 3533)	568*	**<0.001**
Vitamin C (mg)[b]	92.8 (4.35 - 213)	126 (36.3 - 370)	60**	0.05
Vitamin D (µg)[b]	2.52 (0.29 - 9.44)	4.13 (1.45 - 11.0)	10*	**<0.01**
Thiamin (mg)[a]	1.02 ± 0.37	1.25 ± 0.40	0.8*	**0.01**
Riboflavin (mg)[b]	1.08 (0.48 - 2.22)	1.22 (0.72 - 2.53)	0.84*	**0.03**
Niacin (mg)[b]	13.7 (8.48 - 25.1)	14.0 (7.66 - 23.5)	11	0.2
Vitamin B6 (mg)[b]	1.30 (0.62 - 2.29)	1.73 (0.79 - 3.01)	0.93*	0.1
Folic acid (µg)[b]	218 (74.3 - 368)	248 (129 - 534)	380*	**0.01**
Vitamin B12 (µg)[b]	2.39 (0.56 - 4.91)	2.93 (1.04 - 6.90)	2.1*	0.1
Vitamin E (mg)[b]	0.59 (0 - 3.71)	1.33 (0.34 - 5.51)	11*	**<0.01**

β-carotene (µg)[a]	933 (126 - 4749)	2345 (316 - 15081)	3718****	**0.001**
Minerals				
Selenium (µg)[b]	65.4 (31.4 - 115)	78.4 (37.4 - 152)	41*	0.1
Iron (mg)[b]	9.35 (5.77 - 14.0)	11.2 (7.28 - 20.6)	17*	**0.02**
Magnesium (mg)[a]	253 (145 - 461)	310 (168 - 537)	248*	**0.01**
Zinc (mg)[a]	8.12 ± 2.48	9.01 ± 2.98	10*	0.2

[a]Data provided in mean ± standard deviation, T-Student test. [b]Data provided in median ($p05^{th}$-$p95^{th}$), Mann-Withney test. **DRI=** dietary reference intake**; g=** grams. **mg=** milligrams. **RE=** retinol equivalents. **µg=** micrograms. Bold numbers indicate statistical significance (p <0.05) p value: CQ *vs.* HCQ. Energy requirement and macronutrients calculated according to the recommended distribution percentages [26]; ***AI**= adequate intake and ** **RDA**= recommended dietary allowances [27]; *** DRI FAO [28]; **** DRI DII [14].

Variable	Chloroquine (CQ) (n=31)	Hydroxychloroquine (HCQ) (n=31)	DRI	*p* value
Energy (calories)[a]	1372 (1043 - 2026)	1556 (1024 - 2366)	1563 (1358 -1962)	**<0.05**
Fiber (g)[b]	19.5 (8.75 - 42.4)	23.9 (11.2 - 37.4)	30**	**0.02**
Macronutrients				
Carbohydrates (g)[a]	194 ± 57.6	213 ± 55.8	230 (200 - 289)	0.2
Proteins (g)[b]	61.7 (31.7 - 103)	69.9 (38.1 - 107)	68.4 (59.4 - 85.8)	0.1
Total fat (g)[b]	42.8 (27.2 - 78.2)	55.9 (29.1 - 115)	47.7 (41.5 - 59.9)	0.1
Saturated fat (g)[b]	12.2 (6.39 - 25.2)	18.1 (8.47 - 30.7)	11.9 (10.4 - 15.0)	**0.02**
Monounsaturated fat (g)[b]	13.5 (8.44 - 24.7)	16.2 (7.28 - 31.6)	25.8 (22.4 - 32.4)	0.2
Polyunsaturated fat (g)[b]	8.79 (4.91 - 18.8)	10.4 (4.43 - 24.3)	13.8 (12.1 - 17.4)	0.5
Trans fat (g)[b]	0.32 (0.01 - 1.64)	0.51 (0.08 - 1.75)	1.72 (1.49 - 2.16)	0.1
Omega 3 fatty acids (g)[b]	0.52 (0.32 - 1.10)	0.58 (0.34- 5.87)	2.60 (2.26 - 3.27)	0.3
Omega 6 fatty acids (g)[b]	6.84 (4.18 - 17.6)	7.77 (3.89 - 15.9)	11.3 (9.81 - 14.2)	0.7
Cholesterol (mg)[b]	132 (61.8 - 277)	193 (58.5 - 423)	<300***	**0.03**
Vitamins				
Vitamin A (RE)[b]	323 (57.5 - 1510)	789 (238 - 3533)	568*	**<0.001**
Vitamin C (mg)[b]	92.8 (4.35 - 213)	126 (36.3 - 370)	60**	0.05
Vitamin D (µg)[b]	2.52 (0.29 - 9.44)	4.13 (1.45 - 11.0)	10*	**<0.01**

Thiamin (mg)[a]	1.02 ± 0.37	1.25 ± 0.40	0.8*	**0.01**
Riboflavin (mg)[b]	1.08 (0.48 - 2.22)	1.22 (0.72 - 2.53)	0.84*	**0.03**
Niacin (mg)[b]	13.7 (8.48 - 25.1)	14.0 (7.66 - 23.5)	11	0.2
Vitamin B6 (mg)[b]	1.30 (0.62 - 2.29)	1.73 (0.79 - 3.01)	0.93*	0.1
Folic acid (µg)[b]	218 (74.3 - 368)	248 (129 - 534)	380*	**0.01**
Vitamin B12 (µg)[b]	2.39 (0.56 - 4.91)	2.93 (1.04 - 6.90)	2.1*	0.1
Vitamin E (mg)[b]	0.59 (0 - 3.71)	1.33 (0.34 - 5.51)	11*	**<0.01**
β-carotene (µg)[a]	933 (126 - 4749)	2345 (316 - 15081)	3718****	**0.001**
Minerals				
Selenium (µg)[b]	65.4 (31.4 - 115)	78.4 (37.4 - 152)	41*	0.1
Iron (mg)[b]	9.35 (5.77 - 14.0)	11.2 (7.28 - 20.6)	17*	**0.02**
Magnesium (mg)[a]	253 (145 - 461)	310 (168 - 537)	248*	**0.01**
Zinc (mg)[a]	8.12 ± 2.48	9.01 ± 2.98	10*	0.2

[a]Data provided in mean ± standard deviation, T-Student test. [b]Data provided in median ($p05^{th}$-$p95^{th}$), Mann-Withney test. **DRI=** dietary reference intake**; g=** grams. **mg=** milligrams. **RE=** retinol equivalents. **µg=** micrograms. Bold numbers indicate statistical significance (p <0.05) p value: CQ *vs.* HCQ. Energy requirement and macronutrients calculated according to the recommended distribution percentages [26]; ***AI**= adequate intake and ** **RDA**= recommended dietary allowances [27]; *** DRI FAO [28]; **** DRI DII [14].

Figures

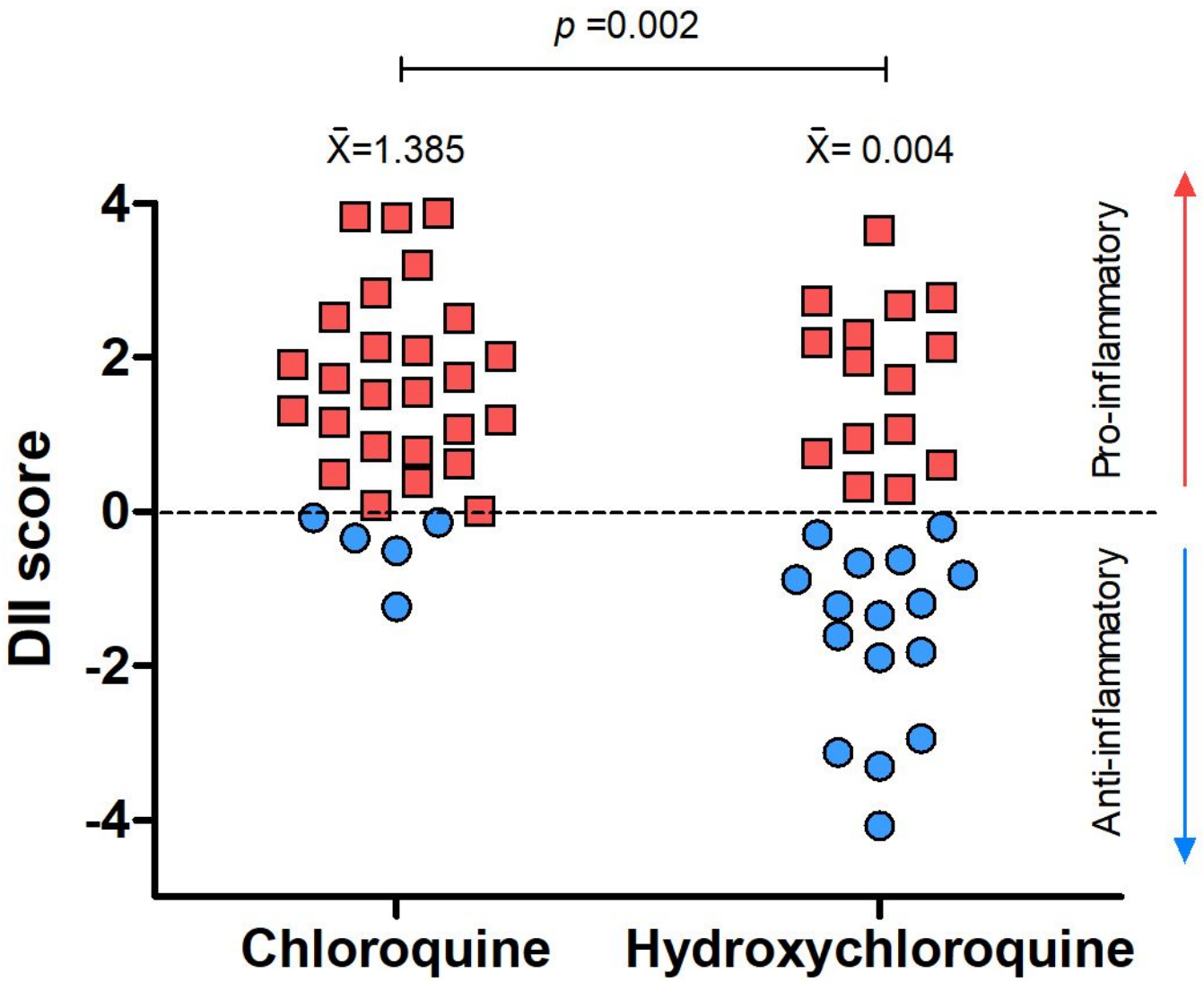

Figure 1

Comparison between the DII scores stratified by antimalarial treatment in SLE patients. Chloroquine= DII: 1.385±1.327 vs. hydroxychloroquine= DII: 0.004±2.024. Data provided in mean ± standard deviation, p value: T student test. Normal distribution: Shapiro-Wilk test.

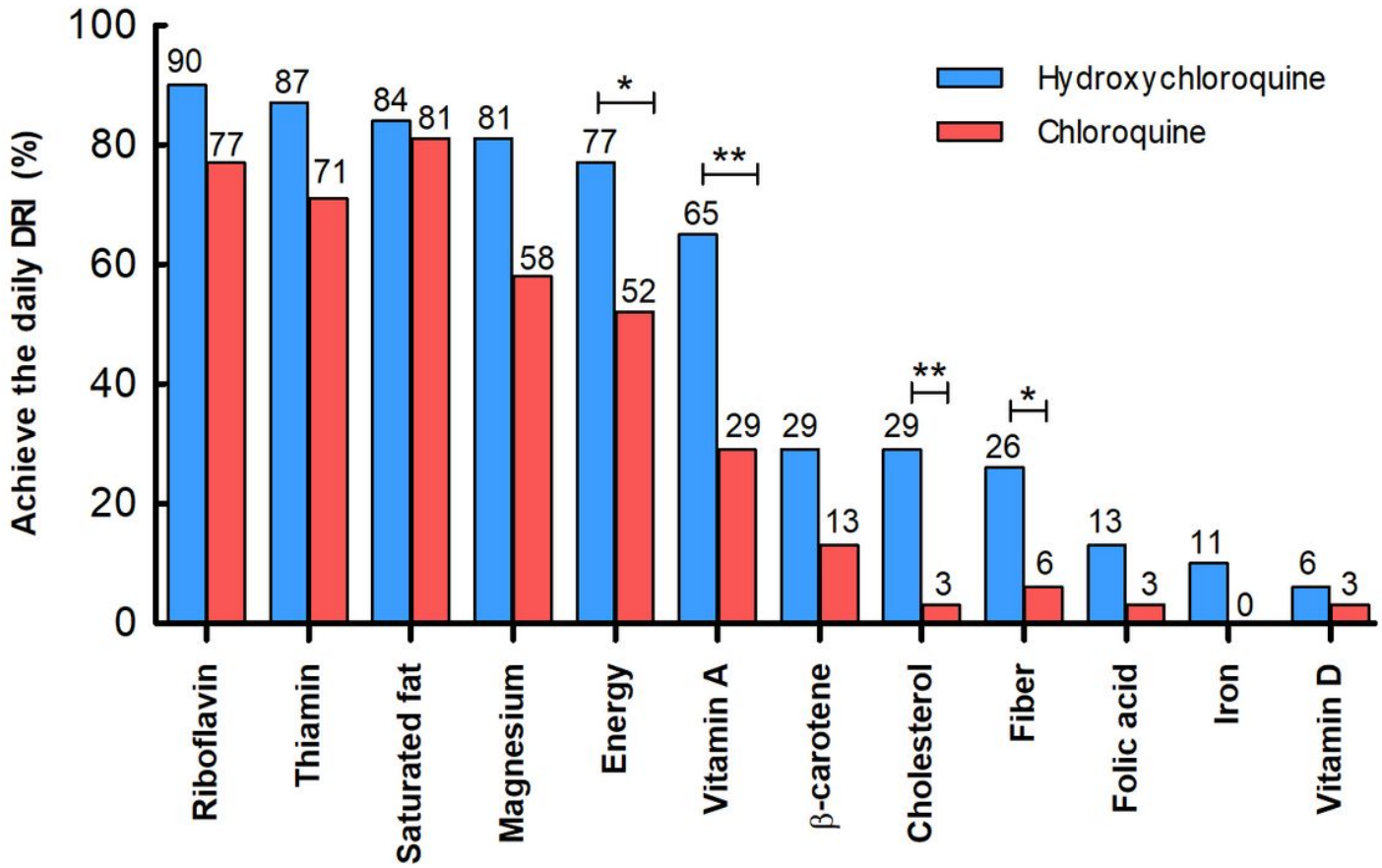

Figure 2

Nutrient intake of SLE patients with antimalarial treatment stratified by the achievement of daily DRI. Data provided in percentages, χ2 test: * p value <0.05 ** p value <0.01. DRI= dietary reference intake: energy and saturated fat according to the recommended distribution percentages [26]; fiber according to RDA= recommended dietary allowances, and vitamin A, vitamin D, thiamin, riboflavin, folic acid, iron and magnesium according to AI= adequate intake [27]; cholesterol <300 mg/day according to DRI FAO [28]; β-carotene according to DRI DII® [14].