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Vitamin D Supplementation Is Associated with Disease Activity in Systemic Lupus Erythematosus Patients †

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† Presented at the 1st International Electronic Conference on Nutrients—Nutritional and Microbiota Effects on Chronic Disease, 2–15 November 2020; Available online: https://iecn2020.sciforum.net/.

Published: 30 October 2020

Abstract: Systemic lupus erythematosus (SLE) is a chronic disease characterized by inflammatory response and abnormal autoimmune disease. Vitamin D is essential in phosphorus-calcium metabolism, has immunosuppressive properties, and is considered a therapeutic option. Controversy exists about the role of this vitamin in the pathogenesis of SLE. Thus, the aim of this study was to investigate the influence of the dietary intake of vitamin D and its supplementation in a cohort of patients with SLE. A cross-sectional study including a total 285 patients with SLE was conducted (248 females and 26 males; mean age 46.99 ± 12.89 years). The SLE disease activity index (SLEDAI-2K) and the SLICC/ACR damage index (SDI) were used to assess disease activity and disease-related damage, respectively. Levels of C-reactive protein (CRP; mg/dL), homocysteine (Hcy; mol/L), anti-double stranded DNA antibodies (anti-dsDNA) (IU/mL), complement C3 (mg/dL), and complement C4 (mg/dL), among other biochemical markers, were measured. The dietary intake of vitamin D and the intake of vitamin D supplement were obtained via a 24-h patient diary. A share of 57.1% of the patients took vitamin D supplements and the average of dietary vitamin D was 2.08 ± 2.94 μg/day. Note that 98.2% of patients did not reach the recommended dietary intakes for vitamin D intake. Multivariate regression analysis revealed that clinical and laboratory variables are not significantly affected by vitamin D intake levels after adjusting for age, gender, energy intake, and medical treatment (immunosuppressants, corticosteroids, and antimalarials). Patients with SLE who took vitamin D supplements had significantly higher serum complement C3 levels compared to patients who did not take them after adjusting for covariates (110.28 ± 30.93 vs. 107.38 ± 24.18; p = 0.018). Our findings suggest a potential impact of supplementation of vitamin D on the activity of SLE. Future longitudinal research on SLE patients, including intervention trials, are required to validate these preliminary data.

Keywords: autoimmune; systemic lupus erythematosus; vitamin D intake; vitamin D supplementation

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens. It is a multisystem disease with heterogenous clinical manifestations including rash, arthritis, fatigue, nephritis, neurological problems, anemia, and thrombocytopenia [1]. The etiology of SLE is unknown although it has been proposed that multiple genetic, immunological, endocrine and environmental factors might play a main role in development and activity [2].

Vitamin D is essential in phosphorus-calcium metabolism, has immunosuppressive properties, and is considered a therapeutic option in autoimmune diseases [3]. Controversy exists about the role of vitamin D in the pathogenesis of SLE although it has been established as an essential element that may be relevant in SLE progression [4]. Recent research has reported that vitamin intake might be linked to SLE because vitamin D deficiency is highly prevalent in SLE patients [4,5]. In addition, vitamin D intake was found to be associated with decreased risk of other autoimmune diseases such as multiple sclerosis [6].

Considering the inconsistent findings and limited evidence regarding potential association between vitamin D intake and SLE activity, and taking into account that SLE has a significant impact on the mortality and morbidity of patients, we aimed to investigate the relationship between the dietary intake of vitamin D and its supplementation, and SLE disease, in a cohort of patients with SLE.

2. Methods

2.1. Study Population

A cross-sectional study was conducted among a population of SLE patients recruited in the Andalusian region of Spain. All patients met the SLE revised criteria of the American College of Rheumatology (ACR) or Systemic Lupus Erythematosus International Collaborating Clinics Group (SLICC) criteria [7,8]. The exclusion criteria were: pregnancy, cerebrovascular disease, ischemic heart disease, active infections, major trauma or surgery in the previous six months, serum creatinine ≥1.5 mg/dL and the presence of other autoimmune and/or chronic diseases not related to the main disease (i.e., type 1 diabetes, multiple sclerosis rheumatoid arthritis, cancer). A total of 258 SLE patients met the inclusion criteria and were included in the study after giving written informed consent (mean age of 46.99 ± 12.89; 90.5% female). The local ethics committee approved the study protocol ("Comité Coordinador de Ética de la Investigación en Andalucía" (30-11-2016)), which was conducted in agreement with the Declaration of Helsinki.

2.2. SLEDAI and SDI Assessment

The activity of the disease was assessed with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [9]. The SLICC/ACR damage index (SDI) was used to measure disease-related organ damage [10].

2.3. Assay of Anti-dsDNA, Complement Levels, hs-CRP and Hcy Determinations

A BioPlex 2200 System (Bio-Rad, Hercules, CA, USA), which automatically detects antibodies to several antigens in one tube, was used to measure Anti-dsDNA titers. Serum samples were obtained to determine quantitatively human complement components C3 and C4 by immunoturbidimetric assay (Beckman Coulter AU System CRP Latex reagent) using a Beckman Coulter analyzer (AU5800 Analyzer, Beckman Coulter, Brea, CA, USA). A highly sensitive technique based on immunoturbidimetric assays was used to measure hs-CRP levels (Beckman Coulter AU System CRP Latex reagent) in a Beckman Coulter analyzer (AU5800 Analyzer, Beckman Coulter, Brea, CA, USA). An enzymatic colorimetric assay was used to determine Hcy serum levels in a Beckman Coulter analyzer (AU680, Beckman Coulter, Brea, CA, USA) with the Axis-Shield Liquid Stable (LS) 2-Part Homocysteine Reagent (Axis-Shield Diagnostics Ltd., Dundee, UK).

2.4. Dietary Intake of Vitamin D and Vitamin D Supplementation

To estimate dietary intake of vitamin D and vitamin D supplementation a 24 h diet recall was used. Pictorial food models and standard household measures were used for better accuracy of the food quantities registered [11]. To convert the reported food and beverage intake into nutrient intake the software "El Alimentador" (Fundación Alimentación Saludable. Madrid, Spain) [12] was used.

2.5. Statistical Analysis

All statistical analyses were conducted using the SPSS® Statistics version 21.0 (SPSS, Chicago, IL, USA) software. Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± standard deviation. To verify data distribution normality the Kolmogorov–Smirnov test was applied. Multivariate regression analysis was used to analyze the association between clinical disease variables and the intake of vitamin D after adjusting for the following covariates: age, sex, energy intake, and medical treatments (immunosuppressants, antimalarials, and/or corticosteroids. *p*-values of <0.05 were taken as statistically significant.

3. Results

The main characteristics of the study population are shown in Table 1. A share of 57.1% of the patients took vitamin D supplements and the average of dietary vitamin D was 2.08 ± 2.94 μg/day. Note that 98.2% of patients did not reach the recommended dietary intakes for vitamin D intake.

Table 1. Description of the main characteristics of the study population.

Characteristics	Total (n = 193)
Female	248 (90.5)
Age (years)	46.99 ± 12.89
Energy (kcal)	1775.03 ± 507.69
Vitamin D intake (μg)	2.08 ± 2.94
Clinical data	
Time since diagnosis (years)	9.11 ± 6.64
Number of complications	3.38 ± 1.34
SLEDAI[a] score	2.65 ± 2.68
SDI score	0.97 ± 1.23
Laboratory markers	
hsCRP (mg/dL)	3.17 ± 4.81
Hcy (μmol/L)	12.48 ± 7.45
Anti-dsDNA (IU/mL)	18.37 ± 37.09
Complement C3 level (mg/dL)	109.17 ± 28.25
Complement C4 level (mg/dL)	22.81 ± 13.56
Medication used	
Vitamin D supplementation	156 (57.1%)
Antimalarial use	217 (79.5)
Immunosuppressor use	102 (37.4)
Corticoid use	108 (39.6)

Data are expressed as mean and range or frequency and percentage. SLEDAI = systemic lupus erythematosus disease activity index; SDI = damage index for systemic lupus erythematosus; hsCRP = high-sensitivity C-reactive protein; Hcy = homocysteine; Anti-dsDNA = Anti-double stranded DNA antibodies.

Multivariate regression analysis revealed that clinical and laboratory variables are not significantly affected by vitamin D intake levels after adjusting for age, gender, energy intake, and medical treatment (immunosuppressants, corticosteroids, and antimalarials) (Table 2). In contrast, patients with SLE who took vitamin D supplements had significantly higher serum complement C3

levels compared to patients who did not take them after adjusting for covariates (110.28 ± 30.93 vs. 107.38 ± 24.18; $p = 0.018$) (Table 2). Unexpectedly, patients with SLE who took vitamin D supplements also had significantly higher homocysteine levels compared to patients who did not take them (13.66 ± 9.50 vs. 11.05 ± 3.18; $p = 0.016$).

Table 2. Beta estimates and confidence intervals for the association between vitamin D intake, vitamin D supplementation, and clinical disease activity parameters in SLE patients.

	Vitamin D Intake (μg)		Vitamin D Supplementation		
Clinical Parameters	**β (95% CI)**	***p*-Value**	**Yes (n = 156)**	**No (n = 117)**	***p*-Value**
Number of complications	0.004 (−0.049, 0.056)	0.895	3.53 ± 1.44	3.17 ± 1.18	0.922
SLEDAI score	0.015 (−0.092, 0.121)	0.784	2.68 ± 2.85	2.57 ± 2.40	0.229
SDI score	0.012 (−0.036, 0.060)	0.623	1.19 ± 1.35	0.66 ± 0.96	0.123
hsCRP (mg/dL)	−0.108 (−0.301, 0.086)	0.274	3.76 ± 5.54	2.29 ± 3.37	0.238
Hcy (μmol/L)	0.339 (−0.052, 0.731)	0.089	13.66 ± 9.50	11.05 ± 3.18	0.016
Anti-dsDNA (IU/mL)	0.493 (−1.013, 1.999)	0.520	21.33 ± 43.41	14.54 ± 26.12	0.938
Complement C3 level (mg/dL)	−0.759 (−1.869, 0.351)	0.180	110.28 ± 30.93	107.38 ± 24.18	0.018
Complement C4 level (mg/dL)	−0.433 (−1.128, 0.261)	0.220	22.53 ± 12.94	23.16 ± 21.41	0.894

SLE = systemic lupus erythematosus; SLEDAI = systemic lupus erythematosus disease activity index; SDI = damage index for systemic lupus erythematosus; hsCRP = high-sensitivity C-reactive protein; Hcy = homocysteine; Anti-dsDNA = Anti-double stranded DNA antibodies. Data are adjusted by age, sex, energy intake, and medical treatment (immunosuppressor, corticoid, and antimalarial use).

4. Discussion

In the present study we found that the supplementation of vitamin D might have a potential impact on the activity of SLE because we found that patients taking vitamin D supplements had significantly higher levels of C3 compared to patients not supplemented. Unexpectedly, we also found that patients with SLE who took vitamin D supplements had significantly higher homocysteine levels. Research in SLE is limited, usually based on a small sample size, and has led to inconsistent findings. In contrast to our results, Mellor-Pita et al. reported no association between vitamin D supplement intake and SLE-related factors, including homocysteine, in forty-seven females with SLE [13]. These discrepancies could be due to differences in the sample size or to heterogeneity in the clinical characteristics of the recruited patients. In addition, it should be noted that our study included a well-characterized cohort of a population with SLE, including patients in an early-stage of the disease and excluding any with severe lupus complications or affected by other autoimmune diseases. However, in previous studies this data has not been specified [13]. Thus, taking into account that the limited prior studies carried out to investigate the effect of vitamin D supplementation on SLE have produced inconsistent findings, to validate our preliminary results, future studies in homogeneous cohorts of SLE patients are required.

In line with previous studies we observed that dietary intake of vitamin D is not associated with clinical and laboratory variables [5]. This finding supports the hypothesis that the dietary intake of vitamin D might have no effect on SLE disease activity. Similarly, Costenbader et al. concluded that vitamin D intake was not associated with risk of SLE in a large prospective cohort of women [5].

This study has some limitations that should be noted. Firstly, it was a cross-sectional study and, as such, was subject to the limitations inherent to this type of design. Secondly, there were also certain limitations derived from the use of the 24 h diet recall technique because it is prone to under-reporting and relies on participant memory [14]. In contrast, it should be noted that we included the use of

medications (antimalarials, immunosuppressors, and corticosteroids), in addition to age, sex, and energy intake, as cofounders because these factors could have influenced the results.

5. Conclusions

In conclusion, patients taking vitamin D supplements had significantly higher levels of C3 compared to patients who were not supplemented, supporting the potential effect of supplementation of vitamin D on the activity of SLE. However, the dietary intake of vitamin D was not associated with clinical and laboratory variables in women with SLE.

Author Contributions: Data curation, M.C.-R., G.P.-G., S.D.O.-R. and I.M.-M.; Formal analysis, M.C.-R.; Funding acquisition, N.O.-C. and B.R.-M.; Investigation, G.P.-G., and S.D.O.-R.; Methodology, G.P.-G., and I.M.-M.; Project administration, B.R.-M.; Resources, B.R.-M.; Software, I.M.-M.; Supervision and N.O.-C.; Validation, M.C.-R.; Writing—original draft, M.C.-R.; Writing—review & editing, N.O.-C. and B.R.-M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the grant PI0523-2016 from "Consejería de igualdad, salud y políticas sociales" (Junta de Andalucía) and is part of the research group LyDIMED "Lupus y Dieta Mediterránea".

Conflicts of Interest: The authors declare no conflict of interest.

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