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Original Research Article

Association between vitamin D and systemic lupus erythematosus disease activity index in children and adolescents: A systematic review and meta-analysis

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Abstract

Purpose: *To undertake a systematic and a meta-analysis in order to determine whether vitamin D is relevant to systemic lupus erythematosus (SLE) in children and adolescents.*
Methods: *PubMed, Embase, Medline, and Cochrane Library were systematically searched from January 1, 1979 to December 30, 2018. Cross-sectional studies were conducted to compare vitamin D, systemic lupus erythematosus disease activity index (SLEDAI), parathormone (PTH), and calcium between children and adolescents with SLE and healthy children and adolescents. The primary outcomes were the vitamin D level and SLEDAI, whereas the secondary outcomes were vitamin D level, vitamin D deficiency level, PTH, and calcium.*
Results: *A total of 98 articles were obtained, among which 7 studies met the inclusion criteria. The results indicate that serum vitamin D level in SLE group was lower than that in the healthy group. Patients with SLE were more vulnerable to vitamin D deficiency than the healthy group. However, correlation analysis indicate that vitamin D level was poorly correlated with SLEDAI (r = -0.04). Subgroup analysis of latitude and economic status was conducted. However, no correlation was indicated. PTH level was higher (p = 0.45), but calcium level was lower in patients with SLE than in healthy controls (p = 0.003). The correlation study indicated a poorly negative correlation between vitamin D and calcium (r = -0.09, p = 0.90), and negative correlation between vitamin D and PTH (r = -0.44, p = 0.26).*
Conclusion: *The results of this meta-analysis suggest that serum vitamin D level does not exhibit any correlation with SLEDAI.*

Keywords: *Systemic lupus erythematosus, Vitamin D, 25-Hydroxyvitamin D, Children, Adolescent*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, which affecting multiple organ systems and involving the production of multiple auto antibodies in serum. SLE is one of the common rheumatic diseases in children. The incidence of SLE in children ranges from 0.36 to 0.60 per 100,000 [1]. In China, the boy-to-girl incidence ratio of SLE is 1: (3.9–5.93). About

15%–20% of SLE are juvenile-onset, 90% of which occur in female patients [2]. SLE is an inflammatory disease associated with multiple factors, including vitamin D deficiency [3], genes, environment, hormone, and immunity, among others. Patients with SLE often show a decrease in vitamin D serum, potentially causing a decline in the immune system.

Vitamin D comes from three sources: ultraviolet radiation, dietary supplements, and food uptake. Sunshine is an important source of vitamin D, which is transformed from the skin cortex. Under ultraviolet radiation with a wavelength of 300–325 nm, 7-dehydrocholesterol from cholesterol is transformed to vitamin D. After binding to vitamin D-binding protein, the precursor is transported to the liver and kidney and hydroxylated into the bioactive form 1,25 $(OH)_2D_3$ [4]. The activated vitamin D exerts different biological effects *in vivo* by contacting or entering a membrane/nucleus vitamin D receptor (VDR) of different target cells. The VDR is widely distributed *in vivo*. The variable region of VDR is also distributed in the teeth, skin, lung, brain, placenta, and liver, apart from organs that are closely associated with calcium–phosphorus metabolism (such as the intestinal tract, skeleton, and kidney). Once it binds with the target gene, conformational change immediately occurs. Fast reaction mediates ligand-dependent transcription factors and regulates gene transcription in target cells [5].

The binding of activated vitamin D to the VDR not only maintains the stability of minerals (such as calcium phosphate) but also meets bone metabolism and bone transformation requirements. An appropriate amount of vitamin D also contributes to the regulation of osteoblasts and thus plays a crucial role in maintaining skeletal and muscular stability. In autoimmune regulation, vitamin D regulates the antigen capture and antigen presentation capabilities of dendritic cells; affects the activities of macrophages, T lymphocytes, and B lymphocytes and corresponding inflammatory factors; and regulates the secretion of cytokines. Vitamin D also promotes and regulates the proliferation, differentiation, and apoptosis of tumor cells in the target organ [6].

The relationship between SLE and serum vitamin D remains inconclusive, which could be attributed to experimental design, study population, statistical method, detection method, and sample size. No systematic evaluation has thus far been reported on the relationship between SLE and serum vitamin D in children. In the current study, data in relevant reports were integrated and quantitatively analyzed to compare the difference in serum vitamin D level between patients with SLE and healthy group. This study also aimed to explore the association between serum vitamin D level and disease activity in SLE patients.

EXPERIMENTAL

Search strategy

PubMed, Embase, Medline, and Cochrane Library were searched from January 1, 1979 to December 30, 2018 by using the following keywords: “systemic lupus erythematosus” “SLE” “vitamin D” “25-hydroxyvitamin D (25 (OH)D)” “children” and “adolescents”. The search aimed to identify published articles and meta-analyses that evaluate the vitamin D level in SLE patients and healthy controls, as well as to determine the correlation between vitamin D and SLEDAI.

Inclusion and exclusion criteria

Trials were selected according to the following criteria: (1) diagnostic criteria for SLE; (2) age between >28 days and 28 years; (3) cross-sectional studies; (4) exclusion of patients with other diseases associated with serum vitamin D levels; and (5) inclusion of healthy people only in the control group. Reviews, case reports, conference abstracts, and unpublished literature were excluded.

Selection of studies

Two researchers independently screened each title and each abstract of all retrieved studies in accordance with the inclusion criteria. Discrepancies were resolved by consistency analysis, otherwise, by the corresponding author.

Data extraction and management

Two researchers independently extracted the following information from each study: name of the first author; publication year and country, participant characteristics, vitamin D metabolism, detection methods; diagnostic criteria, age of participants, disease duration, and correlation coefficients. These data were analyzed using RevMan5.3.

Statistical analysis

To confirm the consistency of the meta-analysis in the enrolled publications exploring the serum vitamin D level in SLE patients and healthy group, the data were expressed as mean ± SD; if the data were expressed as mean ± SEM, the

data were transformed into mean ± SD. The evaluation of vitamin D deficiency in patients with SLE and in healthy controls was conducted as described above. Vitamin D deficiency is recognized that 25 (OH)D < 15ng/mL [7,8].

Pearson correlation coefficient and Spearman's rank correlation coefficient were commonly used in the publications included in the meta-analysis to determine the correlation coefficient between vitamin D and disease activity in SLE. To reduce the statistical deviation, Spearman's correlation coefficient was transformed into the Pearson correlation coefficient. The standard error of the correlation coefficient was calculated using Eqs 2 and 3, and Fisher z-transformation (Eq 1) was applied for each correlation coefficient. Inverse-variance weighting was used to calculate the corresponding confidence intervals. The merged value of the correlation coefficients was transformed into a final correlation coefficient by using the inverse variance method (Eq 4).

$$\text{Fisher's } z = 0.5 \times \ln(1+r)/(1-r) \quad \ldots\ldots\ldots\ldots (1)$$

$$V_z = 1/(n-3) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$S_e = \sqrt{V_z} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

$$\text{Summary } r = (e^{2z}-1)/(e^{2z}+1) \quad \ldots\ldots\ldots\ldots (4)$$

Key: Fisher's z: Fisher test; r: correlation coefficient; V_z: standard error of correlation coefficient; S_e: standard error of correlation coefficient square root.

The data merging model was confirmed based on the result of heterogeneity testing, which used the Q test and inconsistency index (I^2) test. I^2 > 50% or P < 0.05 suggested the existence of heterogeneity, and a random effects model was chosen; if heterogeneity was lower than 50%, a fixed effects model was selected. The software RevMan 5.3 was used to process the data.

RESULTS

Search results and study characteristics

Ninety-eight records were searched through databases, including PubMed, Embase, Medline, Cochrane Library. Owing to duplicate or redundant publication, lack of inclusion criteria in some studies, and non-eligibility based on reviews and conference abstracts, 91 studies were excluded, and seven studies were included (Figure 1). Five studies [9–13] reported the serum vitamin D level in SLE children and the healthy group; three articles [11–13] compared the serum vitamin D deficiency between the two groups; four studies[10,12,14,15] compared the SLEDAI and the serum vitamin D level in SLE (two studies in developing countries and two studies in developed countries; three studies in middle-latitude countries [12,14,15], and one study in low-latitude countries [10]. The baseline characteristics are summarized in Table 1.

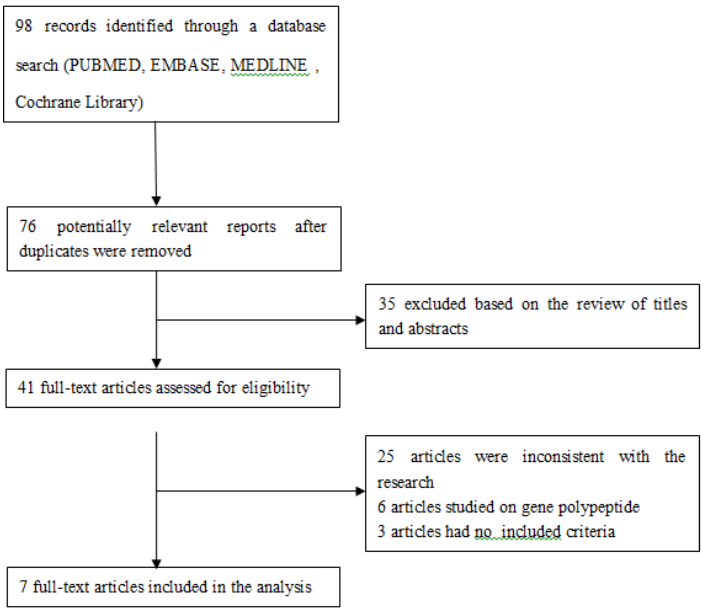

Figure 1: Study flow

Serum vitamin D levels in SLE and healthy controls

Five articles reported the serum vitamin D level, the SLE group was lower than that in healthy controls (Figure 2A, I^2 = 86%, p = 0.0002, MD = -8.44, 95% CI = -12.81 ~ -4.07). In addition, three studies reported vitamin D deficiency in patients with SLE and healthy controls. Compared with healthy controls, patients with SLE were more vulnerable to vitamin D deficiency (Figure 2B, I^2 = 0%, p<0.00001, RD = 0.28, 95% CI = 0.18 ~ 0.38).

Association between vitamin D and SLE disease activity

The Spearman's or Pearson coefficients of serum vitamin D and SLEDAI were selected and calculated. Correlation analysis indicated that vitamin D level was poorly correlated with SLEDAI (Figure 3A, r = -0.04, p = 0.95). Subgroup analysis of latitude and economic status was conducted to confirm the association between SLEDAI and 25(OH)D. However, no correlation was indicated (Figure 3B, 3C, r = -0.04, p = 0.95).

Table 1: Baseline characteristics of the included trials and participants

Study	Year	Country	Vitamin D metabolism	Detection	Diagnostic criteria	No. of patients with SLE	Age (years)	Disease duration (years)	R
AlSaleem [9]	2015	Saudi	25(OH)D	LC/MS/MS	1997 ACR	28	9.7±3.2	5.4±4.3	NM
Rosiles [13]	2015	Mexico	25(OH)D	LC/MS/MS	2005 SLE	37	14.16±2.23	4.0±1.0	NM
COMAK [14]	2014	Turkey	25(OH)D	ELISA	1997 ACR	16	14.47±3.25	2.5±1.0	0.711*, -0.59**, 0.68***
Peracchi [11]	2014	Brasil	25(OH)D	ECLIA	1997 ACR	30	13.7±2.75	3.4±2.9	-0.247*, 0.305***,
Robinson [15]	2012	America	25(OH)D	MS	1997 ACR	24	15.4±3.8	2.5±2.7	0.283*
Wright[12]	2009	America	25(OH)D	RIA	1997 ACR	38	16.0±2.1	NM	0.248*, 0.3542**,
Hamza [10]	2011	Egyptian	25(OH)D	ELISA	1982 ACR	60	12.83±3.05	1.1±0.8	-0.91*, -0.83**, -0.87***

* = r^D value, ** = r^p value, *** = r^c value; *LC/MS/MS: liquid chromatography tandem mass spectrometry; ELISA: enzyme-linked immunosorbent assay; ECLIA: electrochemiluminescence immunoassay; MS: mass spectroscopy; RIA: radioimmunoassay; NM: not mentioned; r^D: the correlation coefficient between vitamin D and SLEDAI; r^P: the correlation coefficient between vitamin D and PTH; r^C: the correlation coefficient between vitamin D and Ca*

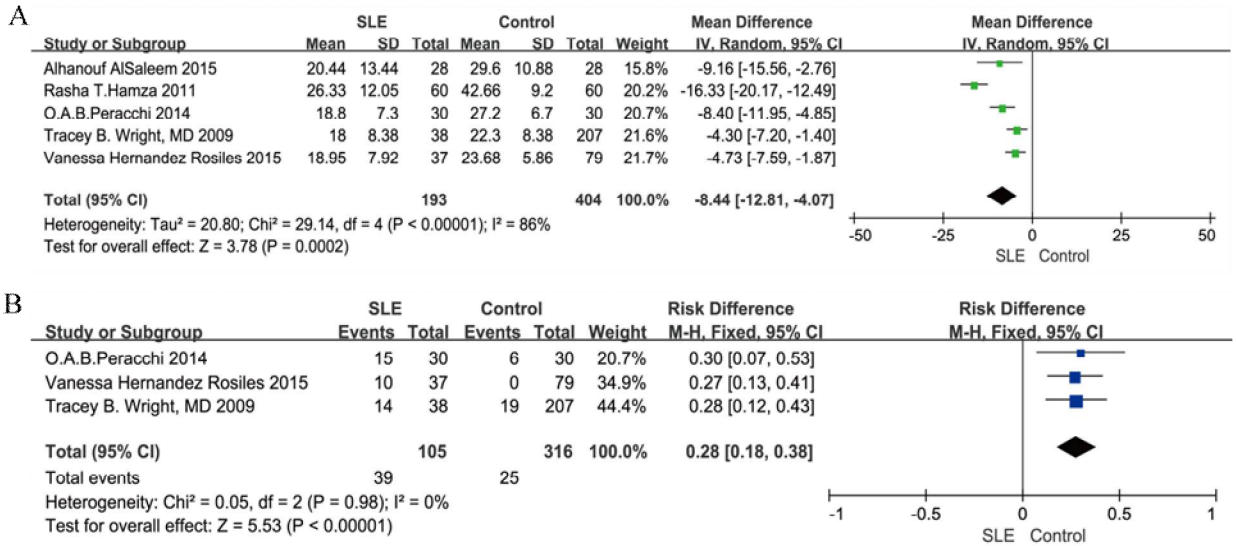

Figure 2: Forest plot of the comparison of vitamin D level between patients with SLE and healthy controls; (B) Forest plot of the comparison of serum vitamin D deficiency level in SLE and healthy controls

Association between vitamin D and laboratory indicators

No difference in PTH was found between SLE patients and healthy controls (Figure 4A, I^2 = 53%, p = 0.45, MD = 1.93, 95% CI = -3.07–6.94). In addition, three studies reported that compared with healthy group, patients with SLE were more vulnerable to calcium deficiency (Figure 4C, I^2 = 87%, p = 0.003, MD = 0.49, 95% CI = -0.82 – -0.16). Correlation analysis indicated that vitamin D level was negatively with PTH, but no significant difference was found (Figure 4B, r = -0.44, p = 0.26). Vitamin D level was poorly

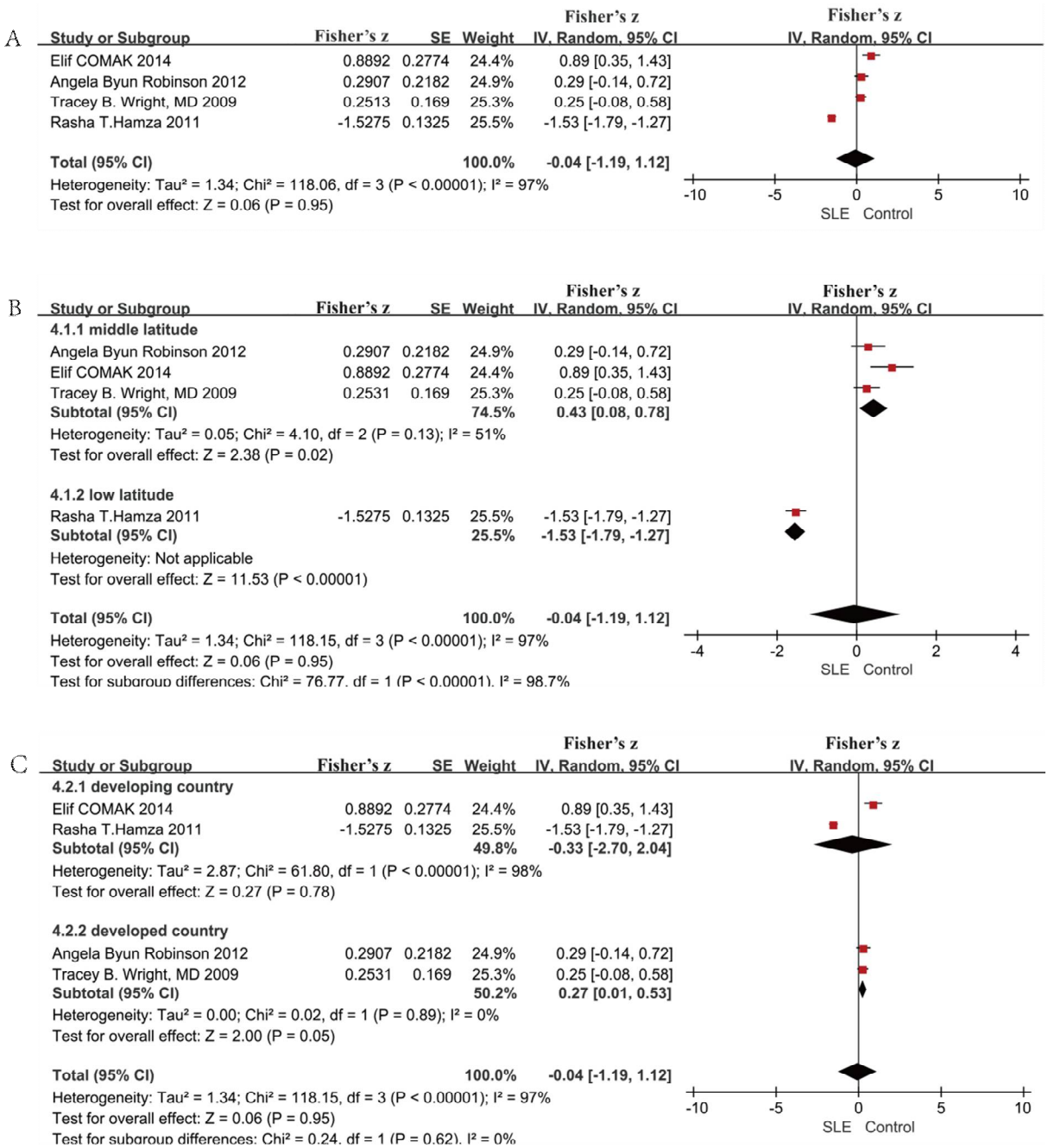

Figure 3: Forest plot of associations between vitamin D and SLEDAI and subgroup analysis (A) vitamin D *vs.* SLEDAI; (B) latitude subgroup analysis; (C) economic subgroup analysis

correlated with Ca level (Figure 4D, r = -0.09, p = 0.90) in patients with SLE.

Publication bias

Publication bias is shown graphically using Funnel plots in Figure 5 in which one study has publication bias.

DISCUSSION

Epidemiological surveys indicate that vitamin D deficiency is closely associated with numerous chronic diseases, such as autoimmune diseases, cancer, cardiovascular diseases, diabetes, infectious diseases, and so on [16]. A growing number of studies have recently demonstrated that the vitamin D level in SLE patients is significantly decreased [17]. The vitamin D level in patients with SLE negatively correlates with SLEDAI [18,19]; however, no significant correlation is determined. The correlation between immune imbalance in SLE and vitamin D deficiency, as well as that between vitamin D level and disease activity in SLE, remains inconclusive.

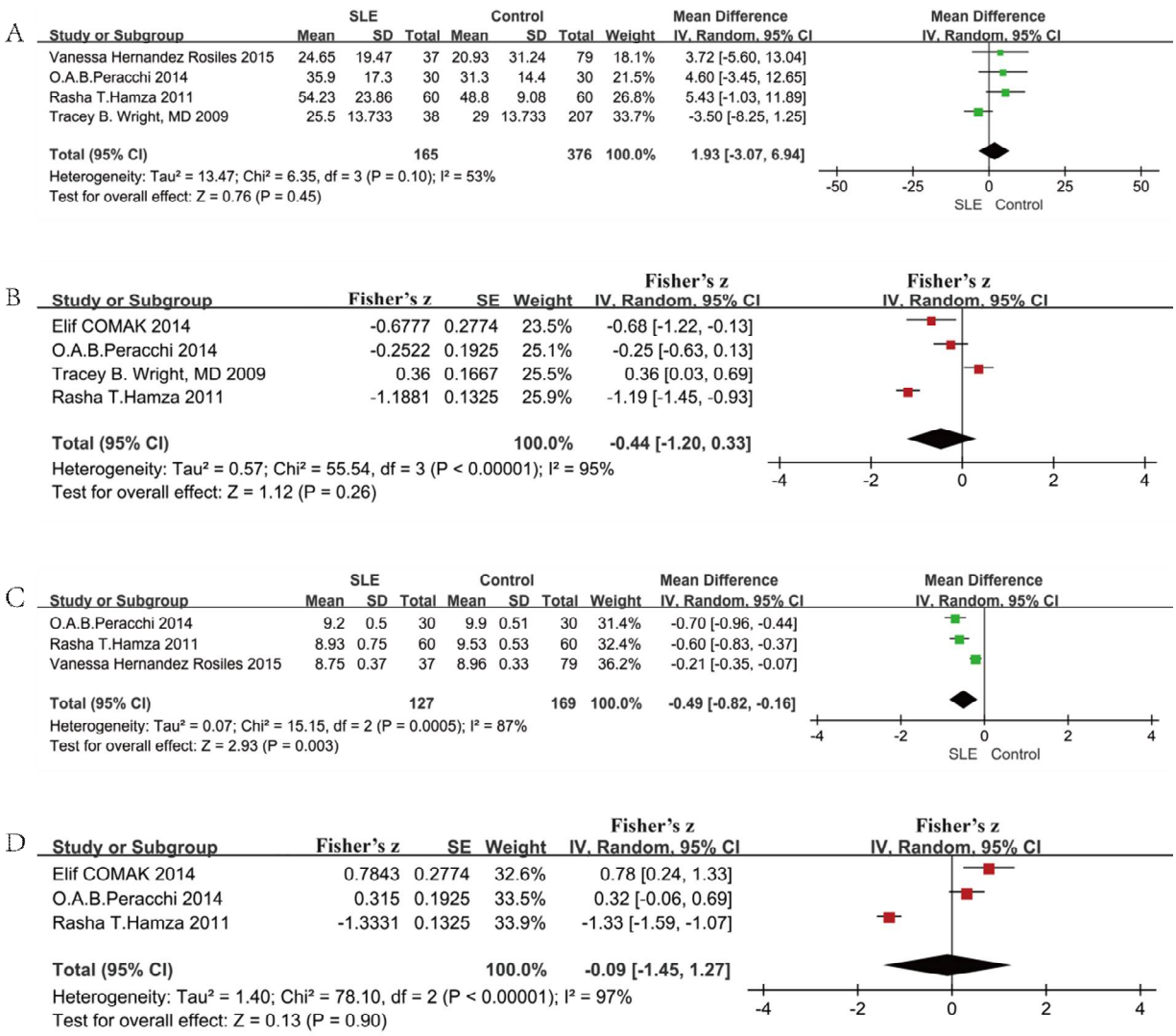

Figure 4: Forest plot of association between vitamin D and laboratory indicators (A) vitamin D *vs.* PTH in SLE and healthy controls; (B) vitamin D *vs.*PTH in SLE; (C) vitamin D *vs.* Ca in SLE and healthy controls; (D) vitamin D *vs.* Ca in SLE

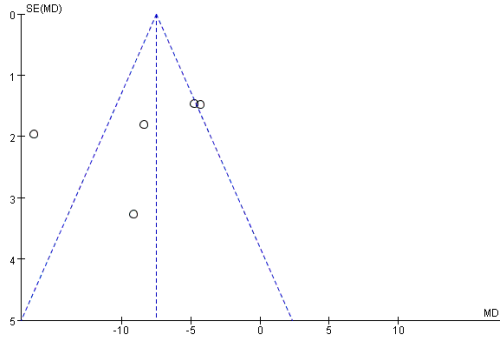

Figure 5: Funnel plot for comparison of vitamin D in patients with SLE and healthy controls

The vitamin D level in the present study is in accordance with *Global Consensus Recommendations* [7,8]. In this guide, 25(OH)D > 20–100ng/mL indicates vitamin D sufficiency; 15–20ng/mL, insufficiency; < 15ng/mL, deficiency; and > 100ng/mL, vitamin D poisoning. The result of the meta-analysis indicated that the serum vitamin D level in patients with SLE was lower than that in healthy controls; in addition, patients with SLE were more vulnerable to vitamin D deficiency, compared with the healthy controls. However, correlation analysis showed that vitamin D level was poorly correlated with disease activity (r = -0.04). Subgroup analysis of latitude and economic status was conducted to confirm the association between SLEDAI and vitamin D; however, no correlation was indicated.

Moreover, $1,25(OH)_2D_3$, the main bioactive form of vitamin D, is synthesized in the kidney using 25(OH) vitamin D-1α hydroxylase, which is mediated by the PTH. The metabolic effect of $1,25(OH)_2D_3$ mediated by the interaction with VDR promotes calcium absorption in the intestinal tract and the kidney and improves the circulation level of calcium. Vitamin D deficiency can promote PTH synthesis, which facilitates

bone adsorption. In the present study, the PTH level was higher (P = 0.45), but the calcium level was lower in patients with SLE than in healthy controls. Correlation analysis showed that 25(OH)D negatively correlates with PTH level and poorly correlates with calcium level (r = -0.09, P = 0.90).

Study limitations

The limitations of this study are as follows: (i) The patients enrolled in the studies were relatively small in number; (ii) The methods used to measure vitamin D in each study varied, resulting in an inappropriate summary of data. However, the included publications were from high-level laboratories, and the selected data were the correlation coefficients with relatively small deviation; (iii) All relevant studies were retrieved as much as possible without language restriction. Funnel plots detected publication bias in one study, leading to exaggeration of results (studies with positive results are more likely to be published than the negative results); (iv) Similar to common types of observational study, the meta-analysis could not interpret causal relationships, unlike meta-analyses of randomized controlled trials (RCTs). However, even RCTs have difficulty overcoming the challenges in the current study. Short-term ultraviolet contact could induce a significant elevate in the 25(OH)D level and remain the same for 2–3 weeks. Without considering the effect of sunshine exposure, measurement of 25(OH)D may lead to a significant bias; and (v) Bias in therapeutic strategy cannot be corrected owing to data restrictions.

CONCLUSION

The result of this meta-analysis suggests that serum vitamin D level does not correlate with SLE activity. A prospective RCT with a large sample size and a detailed design has to be conducted to interpret the correlation between serum vitamin D level and SLE activity, as well as to provide an improved therapeutic strategy.

DECLARATIONS

Acknowledgement

We thank the authors of the included studies for the clarification of existing data.

Conflict of interest

No conflict of interest is associated with this study.

Authors' contributions

We declare that this work was undertaken by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Hongai Liu and Xiaohui Zhang performed the literature search, data analysis, writing, and submission of the manuscript. Xianrong Yang and Xin Jia assisted in the translation, data processing and analysis, literature search, and editing of the manuscript. #Hongai Liu and Xiaohui Zhang contributed equally to this work and should be considered co-first authors.

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