Association between non-dipper hypertension and vitamin D deficiency in women with systemic lupus erythematosus

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Abstract

Objective

Blood pressure (BP) physiologically declines more than 10% at night. Subjects who do not experience this drop are classified as non-dippers. They have a higher risk of cardiovascular diseases (CVD). Vitamin D deficiency and non-dipper pattern have been associated in the general population. Patients with systemic lupus erythematosus (SLE) are more likely to have vitamin D deficiency, a non-dipper pattern and CVD. We aimed to evaluate a possible relationship between vitamin D deficiency and non-dipper pattern in patients with SLE.

Methods

Using 24-hour ambulatory BP monitoring, 77 women with SLE were divided into dippers and non-dippers. 25-hydroxyvitamin D (25(OH)D) levels were compared between both groups. A multivariate analysis was used to determine which variables were independently associated with non-dipper pattern.

Results

62% of patients were non-dippers. They had lower levels of 25(OH)D than dippers (19.4±8.9 vs. 25.9±10.1 ng/ml, p=0.005). Patients with lower 25(OH)D levels were more likely to be non-dippers (OR 3.7, 95%CI 1.2–11.4; p=0.025). The nocturnal decline of mean BP correlated with levels of 25(OH)D (r=0.227, p=0.047). Night-time systolic, diastolic and mean BP inversely correlated with the levels of 25(OH)D (r=-0.274, p=0.016; r=-0.238, p=0.037, and r=-0.260, p=0.022, respectively), but only night- time systolic BP remained significant after adjustment for age and body mass index (r=-0.228, p=0.049). 25(OH)D levels and the use of mycophenolate were found to be independently associated with non-dipper pattern in SLE patients.

Conclusion

Vitamin D deficiency may contribute to the development of a non-dipper pattern in patients with SLE.

Key words

systemic lupus erythematosus, ambulatory blood pressure monitoring, hypertension, non-dipper pattern, 25-hydroxyvitamin D, vitamin D

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Introduction

Over the last two decades, there has been a significant improvement in the understanding of the pleiotropic effects of vitamin D besides bone homeostasis. Indeed, vitamin D receptors have been identified in most human tissues, including cardiomyocytes and vascular endothelial cells (1). Vitamin D deficiency has been associated with several cardiovascular dysfunctions such as arterial stiffness, left ventricular hypertrophy and hypertension (HTN) (2-4). The mechanisms by which vitamin D can reduce blood pressure (BP) are not entirely understood but it seems that it comprises the inhibition of the renin-angiotensin-aldosteron system (RAAS), improvement of the endothelial cell function and decreased parathyroid hormone (PTH) levels that stimulate aldosterone secretion directly by binding to the receptors on the adrenal gland and indirectly by potentiating angiotensin-induced effects (5).

HTN is highly prevalent in patients with systemic lupus erythematosus (SLE) (6). It contributes to the high risk of cardiovascular disease (CVD) (7-9), which is the major cause of mortality in these patients (10). Although the pathogenesis of HTN in SLE is not fully understood, it may occur as a result of a complex interaction between traditional (age, sex, obesity, ethnicity, insulin, homocysteine) and disease- related factors (immune system dysfunction, autoantibodies, inflammation, renal dysfunction and drug side effects) (6, 11-13).

Non-dipping patients have a higher risk of myocardial infarction, stroke and renal dysfunction than subjects with a normal dipper pattern characterised by a BP drop of 10% or more at night (14). There are few studies that explore the role of vitamin D in the pathophysiology of non-dipper HTN. In general, these studies suggest that vitamin D deficiency could be associated with non-dipper pattern and nocturnal HTN in hypertensive patients (15-18). We recently found that women with SLE were more likely to have an adverse night-time BP pattern than controls. In particular, they more frequently presented nocturnal HTN and a non-dipper pattern, which were independently associated with increased arterial stiffness (19). Since vitamin D deficiency is more prevalent among SLE patients than in the general population worldwide (20, 21), we hypothesise that it could also contribute to an altered nocturnal BP pattern in patients with SLE, as occurs in the general population. Thus, the objective of this cross-sectional study was to explore a potential association between vitamin D levels and the non-dipper pattern in patients with SLE.

Material and methods

Participants and protocol

Consecutive, non-pregnant SLE women aged 18–60 years who were followed during at least 1 year were invited to participate. Subjects with a history of overt CVD (acute myocardial infarction, angina pectoris, stroke or peripheral arterial disease), diabetes mellitus, sleep disorders, tachyarrhythmia or with a body mass index (BMI) ≥40 kg/m^2 that could hinder 24-hour ambulatory BP monitoring (ABPM) measurement were excluded. All participants were Caucasian. The Institutional Review Board of our hospital approved the study and all subjects gave written informed consent.

Patients were evaluated using a standardised clinical interview. Fasting blood specimens for biochemical and immunological tests were collected and routinely processed using the techniques performed by the central laboratory of our hospital. In particular, 25-hydroxyvitamin D (25(OH)D; vitamin D) dosing was performed using the chemiluminiscence method by a LIASON Vitamin D assay (Diasorin Inc., Stillwater, Minnesota, USA). The normal range for vitamin D levels in our hospital is between 30 and 100 ng/ml according to the reference literature (1). Blood samples for the measurement of 25(OH)D were obtained between March and October, which corresponds to the higher ultraviolet light period. Additional information necessary for the study was obtained from medical records. Office HTN was deemed to be present if systolic BP (SBP) was >140 mmHg and/or diastolic BP (DBP) was >90 mmHg or if the subject was taking medication for HTN. BMI was calculated using

the following formula: weight (in kg) divided by height (in meters) squared, and obesity was defined as a BMI ≥30 kg/ m^2. The estimated glomerular filtration rate (eGFR) was automatically calculated using the Modification of Diet in Renal Disease (MDRD)-7 equation (http:// www.semergencantabria.org/calc/cacalc.htm). An eGFR <60 ml/min/1.73 m^2 for three months indicated chronic kidney disease. The homeostasis model of assessment (HOMA-IR) was calculated using the formula (HOMA-IR = glucose (mmol/l) x insulin (μU/l / 22.5). Metabolic syndrome was defined according to the revised National Cholesterol Education Program Adult Treatment Panel III criteria (22). Disease activity and cumulated organ damage were measured using the SLE Disease Activity Index (SLEDAI) SELENA modification (23) and SLICC/ACR Damage Index (SDI) (24).

24-hour ABPM measurement and dipping status

24-hour ABPM (SpaceLabs 90207) was done according to the international recommendations (25) and as we have been previously detailed (19). Daytime and night-time periods were defined individually according to each patient's self-reported data of going-to-bed and getting-up times. In treated hypertensive patients, BP-lowering drugs were discontinued 24 hours before the ABPM. From the hourly averages of 24-hour ABPM recordings, daytime, night-time, and 24-h averages of SBP, DBP and mean blood pressure (MBP) were calculated for each patient. The night-time SBP decline (%) was calculated as 100 x (1-sleep SBP/awake SBP) ratio. The night-time DBP and MBP declines were calculated analogously. Patients were categorised by the night-time SBP fall as follows: dippers if the fall was ≥10% and non-dippers if it was <10%, according to the criterion of Verdecchia *et al*. (26).

Statistical analysis

The data were presented as the mean (± standard deviation) for continuous variables and as a percentage for categorical variables. The Shapiro-Wilk test was used for the normality distribution of continuous variables. The Student's *t*-test, Mann-Whitney U-test and Chi-square test were use to compare parametric, non-parametric, and categorical variables, respectively. Odds ratios (OR) and 95% confidential intervals (CI) were calculated. A Spearman test was used to correlate 25(OH)D levels and ABPM parameters.

Patients were categorised as having vitamin D deficiency (25(OH)D≤18 ng/ml), vitamin D insufficiency (25(OH)D>18 and <25 ng/ml) and normal vitamin D levels (25(OH)D ≥25 ng/ml). These cut-offs corresponded to tertiles of the 25(OH)D levels. A multivariate logistic analysis was used to determine which explanatory variables were independently associated with non-dipper pattern (dependent variable). The independent variables included in the multivariable analysis were those that reached a *p*-value <0.10 in the univariable analysis. All analyses used a 5% two-sided significance level and were done using SPSS statistical software, v. 15.0 (SPSS, Chicago, IL, USA).

Table I. Characteristics of patients with dipper and non-dipper patterns.

	All patients n=77	Non-dipper n=48	Dipper n=29	p-value*
Age, years	38 ± 10	38 ± 10	37 ± 11	0.566
Body mass index, kg/m^2	25 ± 5	26 ± 5	24 ± 5	0.153
Obesity, n (%)	10 (13)	7 (14.6)	3 (10.3)	0.734
Office HTN, n (%)	30 (39)	24 (50.0)	6 (20.7)	0.015
Office systolic BP, mmHg	118 ± 14	118 ± 14	118 ± 14	0.772
Office diastolic BP, mmHg	76 ± 11	76 ± 10	76 ± 12	0.916
BP-lowering drugs, n (%)	32 (42)	24 (50)	8 (25)	0.061
eGFR, ml/min/1.73 m^2	86 ± 28	83 ± 32	91 ± 21	0.270
CKD, n (%)	10 (13)	9 (19)	1 (3.4)	0.080
Proteinuria, n (%)	11 (14)	7 (15)	4 (14)	1.0
Homocysteine, μmol/l	12.4 ± 5.0	12.7 ± 5.3	11.8 ± 4.5	0.654
HOMA-IR	2.3 ± 2.0	2.2 ± 2.1	2.4 ± 2.0	0.690
Metabolic syndrome, n (%)	11 (14)	8 (17)	3 (10)	0.520
25(OH) vitamin D, ng/ml	21.8 ± 8.9	19.4 ± 7.1	25.9 ± 10.1	0.005
Parathyroid hormone, ng/ml	35.4 ± 20.3	37.5 ± 23.2	31.9 ± 13.8	0.501
Vit D suppl, n (%)	42 (55)	32 (67)	11 (38)	0.033
ESR, mm/h	24 ± 16	25 ± 11	23 ± 15	0.736
C-reactive protein, mg/dl	0.31 ± 0.44	0.34 ± 0.51	0.27 ± 0.26	0.816
Duration of disease, years	10.9 ± 7.4	11.0 ± 6.9	10.8 ± 7.0	0.724
History of LN, n (%)	31 (40.3)	23 (47.9)	8 (27.6)	0.096
Use of HCQ, n (%)	73 (94.8)	47 (97.9)	26 (89.7)	0.147
Use of prednisone, n (%)	46 (59.4)	33 (68.8)	13 (44.8)	0.055
Prednisone dose, mg/day	4.1 ± 4.6	5.5 ± 5.5	2.7 ± 3.5	0.031
Use of MMF, n (%)	21 (27.3)	18 (37.5%)	3 (10.3)	0.016
SLEDAI	2.5 ± 2.1	2.8 ± 2.1	2.0 ± 2.0	0.127
SDI	0.6 ± 1.4	0.8 ± 1.7	0.3 ± 0.7	0.321
C3 complement, mg/dl	91 ± 22	92 ± 22	90 ± 22	0.900
C4 complement, mg/dl	16 ± 8	16 ± 8	16 ± 7	0.833

HTN: hypertension; BP: blood pressure; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; HOMA-IR: homeostasis model of assessment-insulin resistance; 25(OH)D: 25-hydroxyvitamin D (vitamin D); Vit D suppl: vitamin D supplementation; ESR: Erythrocyte sedimentation rate; LN: lupus nephritis; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
*By Mann-Whitney U-test for continuous variables.

Results

Sample characteristics

In this cross-sectional study, 77 women with SLE (mean age: 38±10 years) and an average disease duration of 11±7 years were included. Most of the patients had stable disease with a median SLEDAI score of 2 (0–4), 29% had a SLEDAI score=0 and 92%a SLEDAI ≤4. Also, organ damage was low (SDI: 0 (0–1)). Clinically, the cumulated frequency of lupus nephritis, neurological involvement, haematological involvement, serositis and antiphospholipid syndrome was 40%, 8%, 38%, 26% and 16%, respectively.

Prednisone and hydroxychloroquine were being taken by 59% and 95% of patients, respectively. The median daily prednisone dose was 5.0 (0–6.25) mg/

day, and immunosuppressive drugs were being used by 38% of patients (azathioprine 7%, methotrexate 7%, mycophenolate mofetil (MMF) 27%). Finally, 55% of patients took vitamin D supplementation.

Baseline demographic, cardiovascular and SLE-related characteristics of patients are presented in Table I. Thirty-two patients (42%) were receiving one or more antihypertensive agents. The cumulative frequency of BP-lowering drugs was angiotensin-converting enzyme inhibitors (59%), angiotensin-II antagonists (47%), diuretics (31%), calcium channel blockers (28%) and beta-blockers (25%).

Differences between dipper and non-dipper patients

On the basis of the results of 24-hour ABPM, 62% (48/77) of patients were non-dippers. Table I summarises the baseline demographic and clinical data of the two groups.

Groups were similar with respect to age, BMI, renal function, proteinuria, homocysteine level, HOMA-IR and frequency of metabolic syndrome. Non-dippers had lower levels of 25(OH)D than dippers (19.4±8.9 *vs*. 25.9±10.1 ng/ml, p=0.005), and patients with vitamin D deficiency (25(OH)D <18 ng/ml) were more likely to be non-dippers compared with patients with normal vitamin D levels (25(OH)D >25 ng/ml) (OR 3.7, 95%CI 1.2–11.4; p=0.025). In addition, as shown in Figure 1, the frequency of non-dippers decreased across rising stretches of 25(OH)D levels (vitamin D deficiency, insufficiency and normal level) (p=0.038). Despite this, non-dippers received more vitamin D supplementation compared to dippers (OR 3.0 95%CI 1.1–7.8; p=0.033). Finally, non-dippers were more likely to have office HTN (but not SBP or DBP) compared with dippers (OR 2.2, 95%CI 1.2–17.3; p=0.015) and they tended to receive more antihypertensive drugs (50% *vs*. 25%, p=0.061).

As for the clinical data, no differences were found in the disease duration, SLEDAI, SDI, levels of C3 and C4 complement, C-reactive protein and erythrocyte sedimentation rate. Non-dipper patients tended to have a history of lupus nephritis more frequently (p=0.096). Furthermore, they received a higher daily dose of prednisone (5.5±5.5 *vs*. 2.7±3.5 mg/day; p=0.031) and were more likely to take immunosuppressive drugs (OR 3.5, 95%CI 1.2–10.2; p=0.028), particularly MMF (OR 5.2, 95%CI 1.4–19.7; p=0.016).

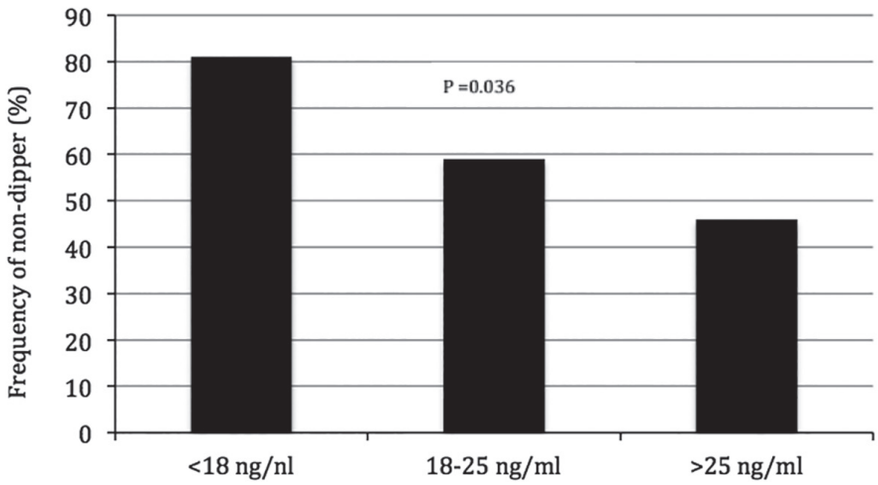

Fig. 1. Frequency of non-dipper pattern according to vitamin D levels.

Table II. Correlation between vitamin D levels with 24-hour ambulatory blood pressure monitoring parameters.

	Rho Spearman	*p*-value
Daytime systolic blood pressure	-0.215	0.061
Daytime diastolic blood pressure	-0.127	0.273
Daytime mean blood pressure	-0.170	0.615
Night-time systolic blood pressure	-0.274	0.016
Night-time diastolic blood pressure	-0.238	0.037
Night-time mean blood pressure	-0.260	0.022
Nocturnal decline of systolic blood pressure (%)	0.189	0.10
Nocturnal decline diastolic blood pressure (%)	0.225	0.049
Nocturnal decline mean blood pressure (%)	0.227	0.047

Table III. Variables independently associated with non-dipping pattern in patients with systemic lupus erythematosus.

	β coefficient	95% coefficient interval	*p*-value
25-hydroxyvitamin D	-0.037	-0.30 – -0.07	0.002
Use of mycophenolate	0.273	0.07 – 0.52	0.01

Correlations between 25(OH)D with 24-hour ambulatory blood pressure monitoring parameters

A significant negative correlation was observed between levels of 25(OH)D and night-time SBP, DBP and MBP (rho:-0.274, p=0.016; rho:-0.238, p=0.037; rho:-0.260, p=0.022, respectively), but only night- time SBP remained significant after adjustment for age and body mass index (r=-0.228, p=0.049). This correlation was not observed with daytime BP (Table II). Moreover, a positive correlation was observed between 25(OH)D levels and a night-time decline in DBP and MBP (rho: 0.225, p=0.049 and rho: 0.227, p=0.047, respectively) and a trend in night-time decline of SBP (rho: 0.189, p=0.10).

Multivariate analysis

The multivariate analysis showed that 25(OH)D (β coefficient -0.037, 95%CI -0.30– -0.07; p=0.002) and MMF use (β coefficient 0.273, 95%CI 0.07–0.52; p=0.010) were associated independently with non-dipper pattern in women with SLE, in a model including vitamin D, history of lupus nephritis (or eGRF), daily prednisone dose (or use

of prednisone), office HTN, and MMF use. The adjusted R^2 value of the model was 0.179 (Table III).

Night-time BP and night-time decline of the BP according to the use of mycophenolate mofetil

The night-time decline of SBP (7.6±6.8 *vs*. 11.2±6.0 %, p=0.016) and of MBP (10.6±7.1 *vs*. 14.4±6.9%, p=0.016) was lower in those patients taking MMF. Conversely, night-time SBP was higher in patients taking MMF compared to those who did not take it (108±9 mmHg *vs*. 102±9 mmHg, p=0.031).

Discussion

As far as we know, the present study is the first that investigates the association between vitamin D deficiency and the presence of a non-dipper pattern and an altered night-time BP decline in SLE. We found that a non-dipper pattern in women with SLE was independently associated with lower levels of vitamin D and the use of MMF. In addition, night-time SBP inversely correlated with vitamin D levels after adjustment for age and BMI, and night-time decline of BP positively correlated with vitamin D levels. Therefore, from a cardiovascular risk point of view, vitamin D deficiency is associated with an adverse night-time BP profile in SLE women.

In the general population, vitamin D deficiency has been associated with increased CVD and cardiovascular risk factors such as HTN (3, 4, 27). Similarly, in SLE patients, vitamin D deficiency has been linked with endothelial dysfunction (21, 28, 29), increased arterial stiffness (30, 31), insulin resistance (31) and CVD (32). In a multinational inception cohort, SLE patients with higher vitamin D levels were less likely to have HTN, even after controlling for age, sex, race, season, country and BMI. Furthermore, over the 11-year follow-up, patients in the higher 25(OH)D quartiles (Q3 and Q4) were less likely to develop an incident cardiovascular event when compared to those in Q1 (32).

Long-term observational studies have established that non-dippers have worse cardiovascular outcomes than dippers (33, 34). Little is known about the effect of vitamin D deficiency on the decline of night-time BP and the non-dipper pattern in the general population. Demir *et al*. (15) reported a strong relationship between non-dipper pattern, lower vitamin D levels and higher PTH levels in hypertensive patients.

Moreover, Yilmaz *et al*. (16) found significantly lower vitamin D levels in patients with non-dipper HTN than in those with dipper HTN, as well as a significant positive correlation between vitamin D and the rate of night-time SBP and DBP decline. Similarly, Karadag and Secen (17) observed lower vitamin D levels and higher PTH levels in non-dippers, as well as a significant positive correlation between vitamin D and night-time BP decline, whereas a significant negative correlation was present between PTH and night- time BP decline. In contrast, Zhang *et al*. did not find any link between vitamin D deficiency and non- dipper HTN but a weak association between night-time DBP (but not SBP) decline and 25(OH) D levels and standing plasma renin activity (18).

Taking into account the increased cardiovascular risk and target organ damage that occurs with non- dipper pattern in the general population (34), these data strengthen the hypothesis that vitamin D deficiency may contribute to a higher cardiovascular risk observed in patients with SLE. However, we cannot establish in our study whether vitamin D deficiency was the cause, the mediator or a biomarker of the adverse night-time BP pattern observed in these patients. Even so, vitamin D deficiency causes secondary hyperparathyroidism (34), decreased endothelial function (36), inflammation (37), decreased inhibition of RAAS activity (38) and increased levels of sympathetic activity (39), which may all cause non-dipper HTN.

As mentioned above, non-dipping patients had lower levels of vitamin D compared with dippers despite receiving significantly more vitamin D supplementation. The daily dose of cholecalciferol received by patients treated with vitamin D supplementation ranged between 400 UI and 800 UI, which correspond to the international recommendations (40). However, regardless of the adherence to treatment, these doses were insufficient to normalise levels of 25(OH)D and reverse the non-dipper pattern in these patients. If higher doses of vitamin D supplementation or analogues are capable of reverting non-dipper pattern and normalising night-time BP then this should be demonstrated in appropriate interventional studies. In this sense, meta-analyses of vitamin D supplementation trials have failed to show clear improvements in BP, and to date the systematic use of the vitamin D or analogues for HTN treatment is not recommended (3). These discrepancies might be due to the heterogeneity of the patients, differences in the sample size and follow-up periods, and the use of different vitamin D doses and dosing intervals. Furthermore, it has been suggested that the link between vitamin D deficiency in patients with CVD and HTN may be an epiphenomenon (3). Thus, low vitamin D levels could merely be associated with HTN through confounding factors such as obesity, low sunlight exposure and low outdoor activity, poor nutrition, and inflammation, among others.

Surprisingly, the use of MMF was associated with a higher frequency of non-dipper pattern, a lower night-time decline of SBP and a higher night-time SBP. Recently, Taylor and Ryan (41) demonstrated that immunosuppression with MMF attenuated MBP in an experimental model of SLE in mice due to the depletion of CD45R+ B cells and the subsequent reduction of autoantibody production, furthering the concept that autoimmunity contributes to the pathogenesis of HTN, but the effect of MMF on night-time BP was not addressed in this study. As far as we know, no other studies have investigated this association. It could be speculated that the use of MMF could be associated with the treatment of more severe manifestations of SLE, especially lupus nephritis, and that this is responsible for the association. Thus, non-dipping patients tended to have more lupus nephritis and to use more prednisone. However, non-dipper pattern was not independently associated with lupus nephritis, chronic kidney disease, proteinuria and parameters of SLE activity or organ damage.

Therefore, we do not have a plausible explanation for this association and further studies are necessary to confirm and explain this finding.

Patients with chronic inflammatory rheumatic diseases, particularly those with rheumatoid arthritis, have 25(OH) D deficiency compared to controls (42). In a large cohort of patients with chronic inflammatory rheumatic diseases, a marginally significant association between 25(OH)D deficiency and anti-citrullinated protein antibodies positivity in patients with rheumatoid arthritis was also found (42). In our study, anti-double-stranded DNA (anti-dsDNA) antibodies did not correlate with 25(OH)D levels.

Moreover, anti-dsDNA antibodies levels were similar in dipper and non-dipper patients.

Some limitations should be considered. The effects of night-time sleep quality on BP dipping were not taken into account. Antihypertensive medications were removed only 24 h before ABPM and a possible residual antihypertensive effect could persist. PTH levels that also may have a role in altered nocturnal BP decline, were not measured. Given the characteristics of the study sample (only female, SLE outpatients with low disease activity and damage who received low prednisone doses and very few immunosuppressive drugs) the results obtained cannot be generalised for all patients with SLE. As a consequence of the relatively small size of the cohort, some statistical significance could not be reached because of a lack of statistical power. Finally, given that ours was a cross-sectional study, conclusions can only be used for hypothesis generation and not as proof of causality.

In conclusion, we found that vitamin D deficiency was associated with the presence of a non-dipper pattern in women with SLE. As occurs in the general population, this abnormal night-time BP decline may contribute to an increased cardiovascular risk documented in patients with SLE. Further large-scale studies are needed to confirm these findings and to evaluate the change in non-dipper status and night-time BP decline in these patients after vitamin D supplementation.

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