Assessment of serum vitamin D level in patients with systemic lupus erythematosus

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Objective
To evaluate the serum level of vitamin D in patients with systemic lupus erythematosus (SLE) and its relationship with disease activity.

Patients and methods
Forty patients suffering from SLE were enrolled in this study (group I). They were further divided into two subgroups according to the SLE disease activity index (SLEDAI) score: group Ia with respect to disease activity and group Ib with respect to disease remission. Another 20 age-matched and sex-matched healthy individuals were chosen as control group II. All patients underwent complete medical history taking and thorough clinical examination; the disease activity was assessed by the use of SLEDAI score. Serum vitamin D level in all patients and controls was measured.

Results
Vitamin D level was significantly higher in controls than in patients. The vitamin D deficiency was highly prevalent among patients with disease activity than in the remission group. There was highly significant inverse correlation between vitamin D level and SLEDAI score in the patient group. Vitamin D level correlated inversely with C reactive protein (CRP) and anti-dsDNA in the disease activity group, whereas it correlated positively with C3.

Conclusion
Vitamin D deficiency is prevalent in SLE patients more than in healthy controls; vitamin D deficiency is highly prevalent among patients with disease activity than in the remission group, and vitamin D level correlated inversely with disease activity, which suggest that inadequate vitamin D level, among other factors, probably contributed to the development of active disease in patients with SLE.

Keywords: disease activity (SLEDAI); systemic lupus erythematosus, vitamin D level

Vitamin D is an essential steroid hormone with well-established effects on mineral metabolism and skeletal health, and with more recently described effects on cardiovascular and immune health [4].

The importance of vitamin D in immune regulation has gained increased interest over the past decade, with the discovery of the vitamin D receptor being expressed by the cells of the immune system and manipulation of 1,25-dihydroxyvitamin D* (1,25(OH)2D) having downstream immune effects. The overall immunologic effects of 1,25(OH)2D include downregulating Th1 immune responses, modulating the differentiation of dendritic cells, and lowering proliferation of activated B cells, whereas upregulating regulatory T cells and preserving innate immune responses. Each of the immune pathways influenced by 1,25 (OH)2D has profound potential implications for patients with SLE [5].

Patients with SLE have multiple risk factors for vitamin D deficiency. The photosensitivity characteristic of SLE determines a lower sun exposure and the use

Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors [1].

Many clinical manifestations of SLE are mediated by circulating immune complexes in various tissues or by the direct effects of antibodies to cell surface components. Immune complexes form in the microvasculature, leading to complement activation and inflammation. Moreover, antibody–antigen complexes deposit on the basement membranes of the skin and kidneys [2]. In active SLE, this process has been confirmed by demonstration of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites. Autoantibodies have been found to be the biomarkers for future neuropsychiatric events in SLE [3].
of sunscreen, which blocks UVB radiation, reducing the skin production of vitamin D. Chronic use of corticosteroids, drugs of frequent use in the treatment of patients with SLE, changes the vitamin D metabolism. In addition, severe renal impairment, which can occur in patients with lupus nephritis, can change the stage of hydroxylation of vitamin D [6].

The purpose of this study was to evaluate the serum level of vitamin D in patients with SLE and its relationship with disease activity.

Patients and method
This study was performed on 40 SLE patients attending the outpatient clinic of Physical Medicine Rheumatology and Rehabilitation Department at Al Zahraa, Al Sayed Galal, and Al Hussein University Hospitals.

The patients were diagnosed according to the 1982 revised criteria of The American College of Rheumatology for the diagnosis of SLE [7]. We classified the patients as group I, in addition to 20 age-matched and sex-matched controls classified as group II. Written informed consent was obtained from all patients and controls for their study participation. The study was approved by the local ethics committee of faculty of medicine for girls.

Exclusion criteria
Patients with other connective tissue diseases, patients with chronic debilitating diseases, and pregnant and lactating patients were excluded from the study.

Clinical examination
Patients were subjected to complete history taking and complete clinical examination, including general, locomotor system, skin, cardiovascular, chest, neurological, and vascular examinations.

Disease activity
The disease activity was assessed in SLE patients by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [8]. Patients with SLEDAI score of more than 6 are considered in a state of active disease (group Ia) and patients with SLEDAI score of less than 6 are considered in a state of inactive disease (remission) (group Ib).

Laboratory assessment
(1) Complete blood profile (assayed by automated counter Sysmex KX-21 N, USA-Mundelein).

(2) CRP using AVITEX CRP (rapid latex agglutination test kit, B00BA-Omega diagnostics, Burlington/ontario).

(3) Erythrocyte sedimentation rate (ESR) using the Westergren method.

(4) Complete urine analysis and total protein (g) in 24-h urine collection.

(5) ANA by ELISA technique.

(6) Anti-dsDNA autoantibody by ELISA technique using Calbiotich kits (CAT NO DDO37G lifescience company USA-CA).

(7) Serum complement (C3) by single radial immunodiffusion method using Astra Formedic C3 Monorid plates (Astra diagnostic, Milano).

(8) Measurement of serum vitamin D level by the immunodiagnostic enzyme immunoassay kits (REF K 2110 Arbeitsanleitung company Australien). Principle of the test according to Wielders and Wijnberg [9].

This test kit is a competitive protein-binding assay for the measurement of 25-OH vitamin D. It is based on the competition of 25-OH vitamin D present in the sample with 25-OH vitamin D tracer for the binding pocket of vitamin D-binding protein (VDBP, Gc-globulin). As all circulating 25-OH vitamin D is bound to VDBP in vivo, samples have to be precipitated with precipitation reagent to extract the analyte. The supernatant can be used without further treatment within the test. In the first incubation step, sample, calibrator, control, VDBP, and the VDBP antibody, an antibody specific for this protein, are added to the solid phase. 25-OH vitamin D present in the sample then competes with the tracer, coated on the well, for the specific binding site of the binding protein, and the VDBP antibody is bound to the vitamin-binding protein. After a washing step to remove unbound components, the quantitation of VDBP is achieved by incubation with a host-specific peroxidase-labeled antibody using tetramethylbenzidine as enzyme substrate. An acidic stopping solution is then added to stop the reaction. The color converts to yellow. The intensity of the yellow color is indirectly proportional to the concentration of 25-OH vitamin D in the sample. A dose–response curve of the absorbance unit versus concentration is generated using the results obtained from the calibrators. Concentrations of 25-OH vitamin D, present in the patient samples, are determined directly from this curve.

Information from the American Society for Bone and Mineral Research (ASBMR 2006) on 25-OH vitamin D are as follows:

(1) Deficiency (seriously deficient): less than 12 ng/ml, respectively, less than 30 nmol/l.
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(2) Insufficiency (deficient): 12–30 ng/ml, respectively, less than 30–75 nmol/l.
(3) Sufficiency (adequately supplied): more than 30 ng/ml, respectively, more than 75 nmol/l.
(4) 1 ng/ml = 2.5 nmol/l
(5) 1 nmol/l = 0.4 ng/ml

The statistical analysis was carried out using statistical package for social science (version 16). Quantitative variables were described by mean ± SD and range (maximum−minimum).

Qualitative categorical variables were described by proportions and percentages.

Data were analyzed using the independent samples t-tests for comparing two groups and one-way analysis of variance (ANOVA) in case of three groups followed by the Scheffe multiple comparison procedure.

Determination of the extent that a single observed series of proportions differs from a theoretical or expected distribution was performed by the χ²-test.

Pearson correlation coefficient was used to measure correlation.

P value greater than 0.05 was considered nonsignificant, P value less than 0.05 was considered significant, and P value less than 0.01 was considered highly significant.

Results

Demographic data of the patient and control groups
This study was performed on 40 SLE patients (group I), 38 female patients (95%) and two male patients (5%). Their ages ranged between 16 and 45 years with a mean of 29.75 ± 6.93 years, and the disease duration ranged from 0.8 to 19 years with a mean of 5.23 ± 4.21 years.

They were diagnosed according to the 1982 revised criteria of The American College of Rheumatology for the diagnosis of SLE [7]. In addition, 20 age-matched healthy controls (group II) were included, 18 female patients (90%) and two male patients (10%). Group I was classified according to the systemic SLEDAI into two subgroups: group Ia included 20 patients with disease activity (SLEDAI>6), 18 (90%) female patients and two (10%) male patients with mean age of 27.90 ± 5.88 years, and group Ib included 20 patients with remission (SLEDAI≤6), all female patients with mean age of 29.90 ± 6.85 years.

Clinical manifestations of SLE
The most frequent clinical manifestations among patients of group I were photosensitivity 52.5% (21 patients) and mucocutaneous manifestations [rash 57% (23 patients), mucosal ulcers 45% (18 patients), and alopecia 42.5% (17 patients)]. Cardiac, renal, and pulmonary involvements were 30% (12 patients), 27.5% (11 patients), and 25% (10 patients), respectively. Musculoskeletal manifestations were: arthritis 28% (11 patients) and myositis 15% (six patients). Fever was found in 23% (nine patients) and CNS involvement was limited in our sample [headache 13%, (five patients), seizures 13% (five patients), and cranial nerves involvement 5% (two patients)] (Fig. 1).

Laboratory investigations among SLE patients
Comparison between group Ia and Ib with respect to laboratory data showed that group Ia patients had significantly higher level of total proteins in 24 h and anti-dsDNA, whereas they had significantly lower C3 level than group Ib patients (P < 0.01). However, there was no statistical significant difference between group Ia and group Ib patients with respect to ESR and CRP (P > 0.05) (Table 1).

Disease activity of SLE patients
On comparing group Ia and group Ib with respect to SLEDAI score, it was revealed that there was high statistically significant difference between the two groups with respect to SLEDAI score (P = 0.000) (Table 2).

Serum levels of vitamin D in the SLE and control groups
Comparison between group I and group II with respect to vitamin D level revealed that vitamin D level ranged from 1.9 to 47 ng/ml in group I (with mean of 11.72 ± 9.08 ng/ml) and 6.4 to 47 ng/ml in group II (with mean of 18.4 ± 12.5 ng/ml) (Table 2).
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13.84 ± 12.16 ng/ml), whereas in group II it ranged from 9 to 42 ng/ml, with mean of 22.37 ± 11.73 ng/ml. There was high statistically significant difference between the two groups ($P = 0.0091$) with higher mean in group II (Table 3).

Vitamin D status in group I and group II: in group I, 27 patients (67.5%) had vitamin D deficiency (<12 ng/ml), seven patients (17.5%) had vitamin D insufficiency (12–30 ng/ml), and six patients (15%) had vitamin D sufficiency (>30 ng/ml), whereas in group II six patients (30%) had vitamin D deficiency, six patients (30%) had vitamin D insufficiency, and eight patients (40%) had vitamin D sufficiency. There was statistically significant difference in vitamin D levels of group I and group II ($P = 0.019$) (Table 4).

**Association between serum vitamin D levels and clinical presentations in SLE patients**

There was significantly lower vitamin D level among patients with photosensitivity, rash, arthritis, and renal involvement in group I and it was highly significantly lower in patients with cardiac involvement, whereas there was no significant difference between vitamin D levels in patients with and without fever, alopecia, mucosal ulcers, myositis, headache, seizures, and pulmonary involvement.

**Vitamin D levels among SLEDAI subgroups**

On comparing group Ia, Ib, and group II with respect to vitamin D level, there was high statistically significant difference between the three groups ($P = 0.000015$) (Table 5).

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**Table 1 Showing comparison between group Ia and Ib with respect to laboratory data**

| Laboratory data                  | Group Ia ($n = 20$) | Group Ib ($n = 20$) | T  | P-value | Significance |
|----------------------------------|---------------------|---------------------|----|---------|--------------|
| Total proteinuria in 24 h        | 0.10–6              | 1.03 ± 1.40         | 0.1–0.32 | 0.17 ± 0.06 | 2.729      | 0.0096        | HS |
| ESR                              | 15–130              | 53.80 ± 32.78       | 17–100 | 37.50 ± 23.41 | 1.810      | 0.0783        | NS |
| CRP                              | 0–48                | 8.15 ± 14.02        | 1–24 | 6.60 ± 5.48   | 0.461      | 0.6477        | NS |
| C3                               | 45–138              | 87.39 ± 27.23       | 97–156 | 118.55 ± 19.78 | -4.140    | 0.0002        | HS |
| Anti-dsDNA                       | 0.4–10              | 4.00 ± 2.91         | 0.2–3 | 1.40 ± 0.92   | 3.807      | 0.0005        | HS |

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HS, highly significant.

**Table 2 Showing comparison between group Ia and Ib with respect to systemic lupus erythematosus disease activity index score**

| Systemic lupus erythematosus disease activity index | Group Ia ($n = 20$) | Group Ib ($n = 20$) | T  | P-value | Significance |
|---------------------------------------------------|---------------------|---------------------|----|---------|--------------|
| SLEDAI score                                      | 7–32                | 16.90 ± 7.41        | 0–6 | 2.85 ± 1.98 | 8.190      | 0.000         | HS |

HS, highly significant; SLEDAI, systemic lupus erythematosus disease activity index.

**Table 3 Showing comparison between group I and group II with respect to vitamin D level**

| Vitamin D level | Group I ($n = 40$) | Group II ($n = 20$) | T  | P-value | Significance |
|-----------------|---------------------|---------------------|----|---------|--------------|
| Vitamin D       | 1.9–47              | 13.84 ± 12.16       | 9–42 | 22.73 ± 11.73 | -2.699    | 0.0091        | HS |

HS, highly significant.

**Table 4 Showing comparison between group I and group II in different vitamin D levels**

| Different vitamin D levels | n (%) | Total | $\chi^2$ | $P$   | Significance |
|----------------------------|-------|-------|----------|-------|--------------|
| Deficiency <12 ng/ml       | 27 (67.5) | 33 | 7.94 | 0.019 | S          |
| Insufficiency 12–30 ng/ml  | 6 (30.0) | 13 |               |       |             |
| Sufficiency >30 ng/ml      | 6 (15.0) | 14 |               |       |             |
| Total                      | 40     | 60    |              |       |             |

**Table 5 Showing ANOVA comparison between group Ia, group Ib, and group II with respect to vitamin D level**

| Groups | ANOVA | N | Range | Mean ± SD | F   | P-value | Significance |
|--------|-------|---|-------|-----------|-----|---------|--------------|
| Group Ia |       | 20 | 1.90–11.30 | 6.79 ± 3.02 | 13.5 | 0.000015 | HS |
| Group Ib |       | 20 | 2.70–47.00 | 20.89 ± 13.78 |       |         |              |
| Group II |       | 20 | 9.00–42.00 | 22.73 ± 11.73 |       |         |              |

ANOVA, analysis of variance.
On comparing mean vitamin D level in group Ia and Ib and in group Ia and II, the difference was highly significant, whereas there was no significant difference on comparing mean vitamin D level in group Ib and II (Table 6).

Correlation between serum vitamin D levels and SLEDAI score, anti-dsDNA, complement C3, age, disease duration, 24 h total proteinuria, ESR, and CRP

Correlative study in group I and subgroup group Ia and group Ib with respect to vitamin D level with SLEDAI score, anti-dsDNA, complement C3, age, disease duration, 24 h total proteinuria, ESR, and CRP showed that, in group I there was highly significant inverse correlation between vitamin D level and SLEDAI score ($r = -0.59$, $P = 0.000$); there was significant inverse correlation between vitamin D level and anti-dsDNA ($r = -0.39$, $P = 0.012$); and there was significant positive correlation between vitamin D level and complement C3 ($r = 0.40$, $P = 0.011$). However, there was nonsignificant correlation between vitamin D level and age ($r = 0.01$, $P = 0.947$), vitamin D level and disease duration ($r = 0.04$, $P = 0.805$), vitamin D level and 24 h total proteinuria ($r = -0.26$, $P = 0.111$), vitamin D level and ESR ($r = -0.04$, $P = 0.784$), and vitamin D level and CRP ($r = -0.19$, $P = 0.244$) (Figs 2–4).

In group Ia, there was significant inverse correlation between vitamin D level and SLEDAI score ($r = -0.54$, $P = 0.015$), vitamin D level and anti-dsDNA ($r = -0.64$, $P = 0.04$), and vitamin D level and CRP ($r = -0.55$, $P = 0.013$). There was significant positive correlation between vitamin D level and complement C3 ($r = 0.45$, $P = 0.045$), whereas there was nonsignificant correlation between vitamin D level and age ($r = 0.12$, $P = 0.627$), vitamin D level and disease duration ($r = 0.06$, $P = 0.791$), vitamin D level and 24 h total proteinuria ($r = -0.10$, $P = 0.685$), and vitamin D level and ESR ($r = 0.000$, $P = 0.994$) (Figs 5–8).

In group Ib, there was a significant inverse correlation between vitamin D level and SLEDAI score only, whereas there was nonsignificant correlation between vitamin D level and age ($r = -0.16$, $P = 0.499$), vitamin D level and disease duration ($r = -0.15$, $P = 0.542$), vitamin D level and 24 h total proteinuria ($r = -0.09$, $P = 0.708$), vitamin D level and ESR ($r = 0.27$, $P = 0.242$), vitamin D level and CRP ($r = -0.20$, $P = 0.404$), vitamin D level and complement C3 ($r = 0.04$, $P = 0.853$), and vitamin D level and anti-dsDNA ($r = -0.09$, $P = 0.709$) (Fig. 9).

Discussion

Although the factors contributing to the pathogenesis of SLE have not yet been completely clarified, genetic mechanisms, and environmental, hormonal, and immune factors are known to be implicated [10]. Among the environmental factors, vitamin D has been the subject of an increasing number of studies in recent years, which have demonstrated its role in autoimmunity [11].

The wide distribution and expression of the vitamin D receptor in most immune cells, such as monocytes, macrophages, dendritic cells, natural

Table 6 Showing multiple comparisons by the Scheffe method

|                | P-value | Significance |
|----------------|---------|--------------|
| Group Ia and group Ib | 0.000175 | HS           |
| Group Ia and group II  | 0.000024 | HS           |
| Group Ib and group II  | 0.844854 | NS           |

HS, highly significant.
killer cells, and T and B lymphocytes, in addition to its effect on cell proliferation and differentiation, makes vitamin D a potential candidate for immune system regulation [12].
Because patients with SLE are advised to avoid direct sunlight, a common trigger of disease flares but also the primary source of vitamin D3, the risk for vitamin D deficiency is even higher among SLE patients than in the general population [13].

This study revealed low vitamin D level in patients with SLE compared with healthy controls. We found also that 85% of our patients had inadequate (insufficient and deficient) vitamin D level (<30 ng/ml), whereas 15% only had sufficient vitamin D level (>30 ng/ml). However, in the control group 60% had inadequate vitamin D level and only 40% had sufficient level. This means that vitamin D deficiency is prevalent in SLE patients more than in healthy controls, although the later group shows relatively high prevalence of deficiency and insufficiency; this was explained by Fragoso et al. [10] to be a result from modern life activities, which make us avoid sun exposure, and consequently reduce vitamin D synthesis.

Our findings are in agreement with those of Damanhour [14] who conducted a study on 165 SLE patients and 214 healthy controls and found that the prevalence of SLE patients with 25(OH) D inadequacy was higher than in the control group: 98.8 versus 55%, 89.7 versus 20% (P < 0.0001). Only two (1.2%) SLE patients had adequate levels of 25(OH) D compared with 96 (45%) individuals of the control group (P < 0.0001). Another study conducted by Handono et al. [15] also found that 20.37% of 54 female patients with SLE had normal vitamin D serum level, 24.7% had insufficiency, and 55.56% had deficiency of vitamin D. In addition, Kamen et al. [16] found lower 25(OH)D in 123 SLE patients when compared with 240 age-matched and sex-matched population controls. In addition, Thudi et al. [17] found that 65% of 25 SLE patients were vitamin D deficient. In contrast, Stockton et al. [18] who conducted their study on 24 SLE female patients and 21 healthy female controls found that there was no significant difference in 25(OH)D levels between groups, and mean 25(OH)D levels of the SLE group was 73.9 nmol/l (29.6 ng/ml). The authors explained that this difference was because this study was conducted in Brisbane, Queensland where ultraviolet radiation levels are high almost all year round; thus, the higher 25(OH)D levels may reflect inadequate photoprotection. It may be also because the mean SLEDAI score of the patients was 4.3, which means that they were in mild activity.

We found that there was lower mean vitamin D level in patients with clinical manifestations compared with patients with no clinical manifestations with respect to photosensitivity, rash, arthritis, and renal involvement with a significant difference, whereas it was highly significant with cardiac involvement. Our findings are in agreement with the study by Ruiz-Irastorza et al. [6] who found that photosensitivity and photoprotection predicted vitamin D insufficiency and deficiency, respectively. They concluded that, being populations in whom photosensitivity and the use of photoprotection are frequent, patients with SLE are at a clear risk of developing 25(OH)D deficiency.

When we classified our patients according to the SLEDAI score into disease activity and remission groups, we found that vitamin D deficiency is highly prevalent among patients with disease activity than in the remission group. All patients with disease activity were vitamin D deficient, whereas 35% of the patients in the remission group had vitamin D deficiency, 35% had insufficiency, and 30% had normal levels. Our result is in agreement with that of Borba et al. [19] who performed a cross-sectional analysis on 36 SLE patients classified according to the SLEDAI score into high activity (group I: 12 patients, mean age 29.6 years) and minimal activity (group II: 24 patients, mean age 30.0 years), and compared them with normal controls (group III: 26 women, 32.8 years). They found that 25(OH) D was significantly different among groups (P < 0.001); group I presented the lowest levels (17.4 ± 12.5) compared with groups II and III with mean levels of 44.6 ± 14.5 and 37.8 ± 13.7, respectively. Handono et al. [15] also conducted their study on 54 female SLE patients in active disease state (SLEDAI score >5) and 23 healthy female controls, and they had found a significant difference between the level of vitamin D in SLE patients and healthy controls (P = 0.000).

In addition, we found an inverse correlation between vitamin D level and disease activity. This relationship was detected in both active disease group (SLEDAI>6) and the remission group (SLEDAL<6). It was significant in both groups, but it was more stronger in the active disease group (r = −0.54, P = 0.015) than (r = −0.51, P = 0.021) in the remission group. In the disease activity group, there was an inverse correlation with vitamin D level, anti-dsDNA, and CRP, whereas there was a significant positive correlation with vitamin D level and C3. We did not find significant correlations between vitamin D level and age, disease duration, ESR, and 24 h proteinuria in both groups. Our results are in agreement with those of Amital et al. [20] who conducted their study on 378 SLE patients: 278 of them had SLE disease activity–2000 (SLEDAI-2K) scores and 100 patients had European Consensus Lupus Activity Measurement scores. They demonstrated a significant inverse relationship between the degree of SLE activity and serum vitamin D concentration. Although the relationship was weak, it was statistically significant, implying that vitamin D
insufficiency, among other factors, probably contributes to the development of active disease in patients with SLE. However, they did not find correlations between vitamin D level and age and disease duration. Another study by Ruiz-Instarozza et al. [6] did not find relationship between vitamin D level and disease duration. Mok et al. [21] in their study on 290 SLE patients found that 25(OH)D3 level correlated inversely and significantly with clinical SLE activity and anti-dsDNA titers. Ben-Zvi et al. [22] found that vitamin D level correlated inversely with disease activity measured by the SLEDAI score ($r = -0.234$, $P = 0.002$) in 198 SLE patients.

We concluded that vitamin D deficiency is prevalent in SLE patients more than in healthy controls; vitamin D deficiency is highly prevalent among patients with disease activity than in the remission group; and vitamin D level correlated inversely with disease activity, which suggest that inadequate vitamin D level, among other factors, probably contributes to the development of active disease in patients with SLE.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

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