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Vitamin D receptor expression level in patients with SLE and its relationship with vitamin D status, disease course and bone mineral density

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ABSTRACT

Objective To determine vitamin D receptor (VDR) blood serum concentrations in patients with SLE and to assess the relationship with vitamin D status, disease course, bone turnover markers levels and bone mineral density (BMD).

Methods The cross-sectional study involved 99 patients with SLE and 30 controls. We assessed VDR, vitamin D, C-reactive protein (CRP), interleukin (IL) 6, osteocalcin (OC), C-terminal telopeptide of type I collagen (CTX) concentrations, and erythrocyte sedimentation rate (ESR) in study subjects. Dual-energy X-ray absorptiometry was also performed.

Results Mean VDR levels in patients with SLE and in the control group were 12.78±0.61 ng/mL and 23.12±0.61 ng/mL, accordingly ($p<0.01$). 77.8% patients with SLE had low VDR concentrations and only 22.2% patients presented relatively normal or high levels. Low VDR levels in patients with SLE were associated with age ($p=0.054$, $r=-0.22$). The study did not reveal a relationship between VDR level and sex, disease duration, body mass index (BMI) and cumulative glucocorticoid (GC) dose. No association was found between VDR level and a diagnosed lupus nephritis, creatinine concentration and glomerular filtration rate. The correlation analysis confirmed the association of low VDR level with high disease activity, namely with elevated CRP ($r=-0.22$), IL-6 ($r=-0.21$) levels, SLE Disease Activity Index 2000 variant ($r=-0.20$). VDR concentration was closely associated with vitamin D supply. The average level of vitamin D in patients with low VDR was 33.55% lower than in the group with a relatively normal vitamin concentration ($p=0.0001$, $r=0.47$). We revealed a proportional increase of CTX concentration associated with VDR decrease ($p<0.05$, $r=-0.27$). No significant difference in average Z-score, T-score and BMD between the groups of patients with SLE with low and relatively normal VDR levels ($p>0.05$) was found.

Conclusion Low VDR concentration is a common phenomenon in patients with SLE associated with age, high disease activity, vitamin D supply and serum CTX concentration. VDR concentration had no significant association with sex, disease duration, cumulative GC dose, BMI, a diagnosed lupus nephritis, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, OC level and BMD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It has been established that vitamin D deficiency and insufficiency are significantly more common in patients with SLE than in practically healthy individuals and are associated with high activity of the inflammatory process, severity of organ damage, changes in bone turnover markers and a decrease of bone mineral density (BMD).

⇒ However, the information about the role of vitamin D receptor (VDR) expression in vitamin D supply, adverse disease course and BMD changes is quite limited for now.

WHAT THIS STUDY ADDS

⇒ The study findings suggest that 77 (77.8%) patients with SLE demonstrated low VDR level, 21 (21.2%) patients had relatively normal levels, and only 1 (1.0%) main study group subject had a high VDR concentration.

⇒ Low VDR concentration was associated with age, high inflammatory activity (C-reactive protein, interleukin 6, SLE Disease Activity Index), hypovitaminosis D and bone turnover marker—C-terminal telopeptide of type I collagen.

⇒ VDR level had no statistically significant association with sex, disease duration, cumulative glucocorticoid dose, body mass index, a history of lupus nephritis, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, bone turnover marker—osteocalcin, and BMD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of the study allow us to better understand the pathogenetic mechanisms influencing vitamin D and VDR status of patients with SLE.

⇒ The blood serum VDR expression in patients with SLE can be assessed as an additional marker of inflammatory activity and bone resorption.

⇒ In prospect, this may serve the grounds for individual correction of hypovitaminosis D in patients with SLE aiming to reduce disease activity and prevent bone loss.

INTRODUCTION

SLE is a chronic multisystemic autoimmune disease based on insufficiency of immunoregulatory mechanisms caused by a complex of environmental, genetic and epigenetic factors, which leads to excessive production of autoantibodies to parent cells and their elements, followed by damage to organs and tissues.[1] One of the important exogenous risk factors directly influencing SLE onset and exacerbation is vitamin D deficiency, which is much more common in the cohort of patients with SLE than in practically healthy individuals. The population studies show that vitamin D insufficiency and deficiency occur in two out of three and in every fifth patient with SLE, respectively.[2–5] The results of our previous study demonstrated that hypovitaminosis D is closely associated with high activity of the inflammatory process, severity of organ damage, changes in the bone turnover markers and a decrease in bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA).[6]

The active form of vitamin D (1,25(OH)2D3) exerts its effects in the human body by binding to the nuclear vitamin D receptor (VDR), which acts as a ligand-dependent transcription factor.[7] This bond induces both genomic and non-genomic regulation of various biological functions,[8] the mechanism of which is still questioned. The existence of VDR in almost all cells of human tissues accounts for multiple regulatory effects of vitamin D beyond its effect on phosphorus-calcium metabolism, such as control of cell proliferation and differentiation, immune response, angiogenesis and apoptosis.[7 9] A study has shown that cells of the immune system express VDR and CYP27B1 (1α-hydroxylase), indicating the ability of these cells to synthesise the activated form of vitamin D and respond thereto.[10] In view of this, low VDR expression or its functional deficiency preconditioned by polymorphism of the corresponding gene may be a pathogenetic link to the development of autoimmune diseases, including SLE.

For the time being, scientific data on VDR status in patients with SLE are very scarce, and the analysis of published study findings is quite complicated due to different research methods applied, such as quantification of VDR messenger ribonucleic acid (mRNA) expression and VDR protein concentration by PCR and ELISA, respectively. Previous studies have shown a decrease of blood serum VDR concentration in patients with SLE compared with controls.[11–16] It has been reported that VDR mRNA expression negatively correlates with inflammatory markers in patients with SLE, such as the SLE Disease Activity Index 2000 variant (SLEDAI-2K), tumour necrosis factor alpha (TNF-α) and interleukin (IL) 6.[14 16] A more pronounced drop in VDR expression was also observed in patients with a diagnosis of lupus nephritis than in patients without kidney damage.[11] At the same time, the information on a relationship between VDR expression, age and sex of patients with SLE, disease duration, severity, body mass index (BMI) and cumulative glucocorticoids (GC) dose still remains unclear. Moreover, the information on the relationship between serum VDR and vitamin D concentrations is quite contradictory. Despite the evidence of lower VDR expression in certain tissues with vitamin D deficiency, some scientists have not yet found a direct correlation between the studied indicators, which can be explained by the complexity of VDR synthesis and activity regulation mechanisms.[17–19] The study of blood serum VDR concentration relationship with BMD and bone turnover markers is also on the agenda.

The objective of the work is to define VDR expression in patients with SLE and to assess its relationship with vitamin D status, disease course, bone turnover markers and BMD.

MATERIALS AND METHODS

The main group of study subjects consisted of 99 patients with SLE (84 female and 15 male). The control group enrolled 30 individuals, representative for age and sex, presenting neither signs of musculoskeletal disorders nor any evidence that could suggest a diagnosis of rheumatological pathology.

All stages of the study were conducted in compliance with bioethical standards in accordance with the basic WHO provisions, World Medical Association Declaration of Helsinki (1964–2008), The Council of Europe Convention on Human Rights and Biomedicine (1997), The International Code of Medical Ethics of the World Medical Association (1983), and current legislation of Ukraine.

SLE diagnosis was established using the European Alliance of Associations for Rheumatology/American College of Rheumatology (ACR) criteria and formalised according to the classification recommended by the Ukrainian Association of Rheumatologists (2002).[20] The disease activity in the SLE group was assessed using SLEDAI-2K.[21] The degree of damage to internal organs was assessed using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI).[22]

The average age of the patients with SLE was 48.92±1.14 years (22–72). The largest part of the examined patients with SLE (51.5%) fell into the age interval from 45 years to 59 years. The average duration of the disease was 12.2±0.87 years. The disease duration in 50.5% subjects in the main group exceeded 10 years.

Cumulative GC dose was calculated for all patients as a multiplication of the daily GC dose by the number of days of administration for the entire period of SLE treatment and expressed as methylprednisolone equivalent. The average cumulative GC dose for the examined individuals was 43.65±3.34 g. Patients' intake of calcium, vitamin D, immunosuppressants, antiresorptive medicines, and anticonvulsants at the time of enrolment in the study and within 12 months heretofore was considered an exclusion criterion.

See the general characteristics of the study subjects in the main group in table 1.

Table 1 General characteristics of the examined patients with SLE

Criteria	Groups	Patients with SLE (n=99)	
		$n_{абс}$. (%)	M±m
Sex	Women	84 (84.8%)	
	Men	15 (15.2%)	
Age, years	Young age, below 44	34 (34.3%)	48.92±1.14
	Middle age, 45–59	51 (51.5%)	
	Advanced age, 60 and over	14 (14.2%)	
Age at disease onset, years	<25	15 (15.2%)	36.71±1.07
	25–40	43 (43.4%)	
	>40	41 (41.4%)	
Disease duration, years	<5	20 (20.2%)	12.20±0.87
	5–10	29 (29.3%)	
	>10	50 (50.5%)	
Disease course	Acute	1 (1%)	
	Subacute	13 (13.1%)	
	Chronic	83 (83.8%)	
	Newly diagnosed	2 (2%)	
Smoking status	Non-smoker	83 (83.8%)	
	Smoker	16 (16.2%)	
BMI, kg/m²	<18.5	5 (5.1%)	27.37±0.56
	18.5–24.9	31 (31.3%)	
	25–29.9	30 (30.3%)	
	≥30	33 (33.3%)	
Cumulative GC dose, g	<35.04	46 (46.5%)	43.65±3.34
	≥35.04	53 (53.5%)	
Disease activity assessed by SLEDAI-2K, score	No activity (score 0)	3 (3.0%)	13.36±0.50
	Low activity (score 1–5)	1 (1.0%)	
	Moderate activity (score 6–10)	25 (25.3%)	
	High activity (score 11–19)	58 (58.6%)	
	Very high activity (score ≥20)	12 (12.1%)	
SLICC/ACR DI, score	No organ damage (score 0)	1 (1.0%)	3.10±0.14
	Low SLICC/ACR DI Score (1 point)	8 (8.1%)	
	Moderate SLICC/ACR DI Score (2–4 points)	79 (79.8%)	
	High SLICC/ACR DI Score (>4 points)	11 (11.1%)	

BMI, body mass index; GC, glucocorticoid; SLEDAI-2K, SLE Disease Activity Index 2000 variant; SLICC/ACR DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

VDR expression level was determined using the Human VDR (Vitamin D3 receptor) ELISA Kit (Fine Test, People's Republic of China). The choice of ELISA for assessing serum VDR expression was justified by the number of advantages such as non-invasiveness, accessibility, practicality and the possibility of standardising indicators for further practical clinical implications.

The blood serum vitamin D concentration was determined using the 25-OH Vitamin D Total (Vit - D Direct) Test System kit (Monobind, USA). Bodily vitamin D status was characterised as optimal (30–50 ng/mL), insufficient (20–30 ng/mL) and deficient (<20 ng/mL).

Blood C-reactive rotein protein (CRP) concentration was determined by ELISA test using a standard kit Diagnostic Automation (USA). To determine the blood serum level of proinflammatory cytokine IL-6, we performed an ELISA test using a standard kit Calbiotech (Germany).

Blood serum osteocalcin (OC) concentration was determined by ELISA test using the N-terminal midfragment of osteocalcin (N-MID OC) ELISA kit (Immunodiagnostic

Systems Nordic A/S, Denmark). To determine the level of C-terminal telopeptide of type I collagen, we used the ELISA test kit manufactured by Nordic Bioscience Diagnostics A/S (Denmark).

Changes in BMD of the lumbar spine (LS) at the level L1–L4 and of the proximal part (neck and entire proximal part) of the femur were determined by DXA using Hologic Discovery Wi apparatus (S/N 87227) and OsteoSys DEXXUM T densitometer. The BMD findings were presented in absolute BMD values, as well as in the form of T-score and Z-score. BMD is the amount of mineralised bone tissue per unit area of the scanned path (g/cm^2). The T-score was considered the number of SD from the mean peak bone mass of healthy individuals aged 20–29 years, and the Z-score was taken as a number of SD from the normal value for individuals of the same age, sex and ethnicity.

Osteoporosis was diagnosed in postmenopausal women and men over 50 years of age, if T-score of the lumbar vertebrae (L1–L4) or of the proximal femur (femoral neck (FN) and entire proximal femur) was −2.5 SD or less. We used Z-score to determine BMD in women of reproductive age and men below 50 years of age. Z-test score ≤−2.0 SD was interpreted as 'below the expected age norm'.

The IBM programme SPSS Statistics V.27 was used for statistical processing of the results. To establish VDR reference values, we used a percentile analysis method. We used the Shapiro-Wilk test to check the normality of data distribution. Given the abnormal distribution of the study results, non-parametrical methods were used for analysis. The statistical significance of differences between two independent samples was assessed using the Mann-Whitney U test. The Bonferroni-corrected Kruskal-Wallis H test was used for multiple comparisons of independent samples. The Spearman's rank correlation coefficient (r) was used for assessment of the relationship between the values. The level of statistical significance (p)<0.05 was considered a reliable value.

RESULTS

VDR blood serum concentration analysis in the study subjects showed a significant difference between patients with SLE and control group individuals. Given there are no clear criteria for grading VDR expression available in the literature, we conducted a percentile analysis for further evaluation and selected values that corresponded to P_5, P_5–P_{95} and P_{95} of the control group. The optimal VDR concentration was considered to be within the range of 18.28–30.73 ng/mL (P_5–P_{95}), low—below 18.28 ng/mL (<P_5), and high—above 30.73 ng/mL (>P_{95}).

The average VDR level in patients with SLE was 12.78±0.61 ng/mL, while in the control group this indicator was 1.81 times higher and equalled 23.12±0.61 ng/mL (p<0.01). Ranking VDR concentration (table 2) showed that 28 (93.3%) practically healthy individuals demonstrated a relatively normal value, while a low level was detected in 1 (3.3%) of the study subjects. In contrast, only 21 (21.2%) of the patients with SLE had relatively normal VDR serum concentration, and 77 (77.8%) patients with SLE presented low VDR levels. Only one (1.0%) patient with SLE and one (3.3%) individual in the control group demonstrated a high VDR value.

The survey of differences in VDR values with regard to sex in patients with SLE (table 3) showed that the average VDR concentration in women was 6.85% lower than in men (p>0.05). However, the proportions of study subjects in each VDR concentration group were comparable in women and men. For example, 18 (21.4%) women and 3 (20%) men had relatively normal VDR levels. A low value of the studied indicator was found in 65 (77.4%) women and 12 (80%) men. The VDR level was characterised as high in 1 (1.2%) female subject with SLE, and no such cases were found in male patients.

The study of a connection of the blood serum VDR concentration with age of patients with SLE (table 4) showed a trend for lower VDR levels in ageing patients, although the difference in the mean values shown by different age groups was not statistically significant (p=0.054). The VDR levels in middle-aged (45–59 years) and elderly (above 60 years) patients with SLE were 12.19% and 33.08% lower, respectively, than in younger (below 44 years) patients. Also, young patients with SLE were the smallest proportion of individuals with a low VDR level—64.7%. For comparison, middle-aged and elderly patients presented with 80.4% and 100% of low VDR

Table 2 Blood serum VDR values in the control group and patients with SLE

VDR group (by value)	Average level (M±m)	N	% of N
Patients with SLE			
Low level (<18.28 ng/mL)	10.27±0.42	77	77.8
Relatively normal level (18.28–30.73 ng/mL)	20.93±0.67	21	21.2
High level (>30.73 ng/mL)	35.10±0.00	1	1.0
Control group			
Low level (<18.28 ng/mL)	18.00±0.00	1	3.3
Relatively normal level (18.28–30.73 ng/mL)	23.02±0.55	28	93.3
High level (>30.73 ng/mL)	31.00±0.00	1	3.3

VDR, vitamin D receptor.

Table 3 Sex-dependent blood serum VDR values in patients with SLE

Parameter	M±m	VDR, n (%) Low level (<18.28 ng/mL) 1	Relatively normal level (18.28–30.73 ng/mL) 2	High level (>30.73 ng/mL) 3
Female patients with SLE				
n (%)	84	65 (77.4%)	18 (21.4%)	1 (1.2%)
VDR, ng/mL	12.64±0.69	10.24±0.50*	20.09±1.11	35.10±0.00
Male patients with SLE				
n (%)	15	12 (80%)	3 (20%)	0 (0%)
VDR, ng/mL	13.57±1.24	12.08±1.18*	19.57±0.64	–

*Probability of differences compared with the value in the 'relatively normal level' group, determined by Bonferroni-corrected Kruskal-Wallis H test or Mann-Whitney U test in men (p<0.01).
VDR, vitamin D receptor.

values, respectively. The correlation analysis performed by us suggested the statistically significant weak negative relationship between VDR values and age of patients with SLE (r=−0.22).

The study did not reveal a relationship between blood serum VDR concentration and disease duration (table 4). The average VDR levels in groups with different disease duration did not differ significantly (p>0.05). The proportion of individuals with low VDR levels among patients with SLE with disease duration below 5 years was the lowest—65.0%, while the patients with a disease duration of 5–10 years and over 10 years demonstrated proportions of 82.8% and 80.0%, respectively. The correlation analysis also did not reveal a statistically significant relationship between the studied parameters (r=−0.07).

No significant association was found between VDR concentration and BMI in patients with SLE (table 4). Perhaps it is worth noting that mean VDR values in the group with weight deficit were 26.7% and 25.1% lower than those in the normal and overweight groups, respectively. It is noteworthy that among all study groups, the

Table 4 The relationship between VDR concentrations, age, disease duration and BMI of patients with SLE

No.	Age group, years	M±m	VDR, n (%) Low level (<18.28 ng/mL) n=77	Relatively normal level (8.28–30.73 ng/mL), n=2 1	High level (>30.73 ng/mL), n=1
Patient's age, years					
1	Young age, below 44 (n=34)	14.36±1.09	22 (64.7%)	12 (35.3%)	0 (0%)
2	Middle age, 45–59, (n=51)	12.61±0.89	41 (80.4%)	9 (17.6%)	1 (2.0%)
3	Advanced age, 60 and over, (n=14)	9.61±0.50	14 (100%)	0 (0%)	0 (0%)
	Correlation coefficient		−0.22*		
Disease duration					
1	<5 years (n=20)	14.11±1.41	13 (65.0%)	7 (35.0%)	0 (0%)
2	5–10 years (n=29)	12.31±1.22	24 (82.8%)	4 (13.8%)	1 (3,4%)
3	>10 years (n=50)	12.53±0.81	40 (80.0%)	10 (20.0%)	0 (0%)
	Coefficient correlation		−0.07		
BMI					
1	<18.5 (n=5)	8.98±1.78	5 (100%)	0 (0%)	0 (0%)
2	18.5–24.9 (n=31)	12.26±0.90	24 (77.4%)	7 (22.6%)	0 (0%)
3	25–29.9 (n=30)	11.98±1.35	24 (80%)	5 (16.7%)	1 (3.3%)
4	≥30 (n=33)	14.59±0.98	24 (72.7%)	9 (27.3%)	0 (0%)
	Coefficient correlation		0.15		

*Indicates a statistically significant correlation coefficient (p<0.05).
BMI, body mass index; VDR, vitamin D receptor.

Table 5 Relationship of VDR concentration in patients with SLE, GC load and a diagnosis of lupus nephritis

No.	Description	M±m	VDR, n (%) Low level (<18.28 ng/mL), n=77	Relatively normal level (18.28–30.73 ng/mL), n=21	High level (>30.73 ng/mL), n=1	r
Cumulative GC dose						
1	Cumulative GC dose <35.04 g (n=46)	13.43±1.01	32 (69.6%)	13 (28.3%)	1 (2.2%)	−0.17
2	Cumulative GC dose ≥35.04 g (n=53)	12.22±0.74	45 (84.9%)	8 (15.1%)	0 (0%)	
A diagnosis of lupus nephritis						
1	No lupus nephritis (n=45)	13.06±0.87	33 (73.3%)	12 (26.7%)	0 (0%)	
2	Actual lupus nephritis (n=54)	12.56±0.86	44 (81.5%)	9 (16.7%)	1 (1.9%)	
	Creatinine, M±m, µmol/L	86.64±2.60	87.43±3.26	84.02±2.70	80.5	0.115
	GFR, M±m, mL/min/1.73 m^2	78.93±1.80	78.40±2.11	80.89±3.54	79.00	−0.078

r = a correlation coefficient between VDR concentration and the studied indicator.
GC, glucocorticoid; GFR, glomerular filtration rate; VDR, vitamin D receptor.

highest VDR levels were recorded in patients with BMI ≥30 kg/m^2.

To assess the relationship between VDR concentration and GC load (table 5), all patients were divided into two groups against the calculated median cumulative GC dose (35.04 g). The average VDR concentration in the group of patients with SLE who received a cumulative GC dose ≥35.04 g at the time of examination was 9.01% lower than in the group of patients with GC load <35.04 g (p>0.05). Among the study subjects of the main group with a cumulative GC dose <35.04 g, 32 (69.6%) individuals had a low VDR concentration, and 13 (28.3%) patients had a relatively normal one. 45 (84.9%) patients with a cumulative GC dose ≥35.04 g had low VDR concentration, while only 8 (15.1%) patients demonstrated relatively normal readings. The determined correlation coefficient (r=−0.17) indicates a weak negative relationship between VDR concentration and GC load, perhaps not statistically significant (p<0.05).

Blood serum VDR concentration presented no statistically significant relationship with nephritis history in patients with SLE (table 5), perhaps the proportion of patients with low VDR lupus nephritis was 8.2% more than those without a diagnosis of kidney damage. The average concentration of the studied substance in the group of patients without a diagnosis of lupus nephritis was approximately 4% higher than in the group of patients with impaired renal function (p>0.05). No statistically significant relationship was found between blood serum VDR, creatinine concentrations and glomerular filtration rate (GFR).

The study revealed a connection between the inflammatory markers, the severity of organ damage and serum VDR concentration in patients with SLE (table 6). The

Table 6 Relationship between inflammatory activity indicators (ESR, CRP, IL-6, SLEDAI, DI) and blood serum VDR concentration, M±m

Indicator	M±m n=99	VDR concentration: Low level (<18.28 ng/mL) 1 n=77	Relatively normal level (18.28–30.73 ng/mL) 2 n=21	High level (>30.73 ng/mL) 3 n=1	P value	r
ESR, mm/h	21.77±1.41	23.29±1.64*	16.14±2.49	23.00±0.00	0.027	−0.17
CRP, mg/l	9.35±0.26	9.68±0.29*	8.16±0.54	8.90±0.00	0.033	−0.22†
IL-6, pg/ml	15.84±0.44	16.33±0.49*	14.19±1.00	12.60±0.00	0.044	−0.21†
SLEDAI Score	13.36±0.50	13.82±0.50	11.67±1.49	14.00±0.00	0.193	−0.20†
Damage Index Score	3.10±0.14	3.27±0.17	2.57±0.22	1.00±0.00	0.098	−0.19

P value—a probability of difference between groups 1 and 2 by Mann-Whitney U test.
*Statistically significant difference in patients with relatively normal VDR levels.
†Statistically significant value of the correlation coefficient.
CRP, C-reactive protein; DI, Damage Index; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; SLEDAI, SLE Disease Activity Index; VDR, vitamin D receptor.

Table 7 Relationship between vitamin D and VDR concentrations in patients with SLE and the control group

Vitamin D concentration	VDR concentration		
	Low level (<18.28 ng/mL)	Relatively normal level (18.28–30.73 ng/mL)	High level (>30.73 ng/mL)
Patients with SLE	n=77	n=21	n=1
Optimal level (30–100 ng/mL), n=10	4 (40%)	5 (50%)	1 (10%)
Insufficiency (20–29 ng/mL), n=20	12 (60%)	8 (40%)	0 (0%)
Deficiency (<20 ng/mL), n=69	61 (88.4%)	8 (11.6%)	0 (0%)
M±m, ng/mL	16.36±0.80*	24.62±1.40	30.50
P value	0.0001		
Correlation coefficient	0.47†		
Control group	n=1	n=28	n=1
Optimal level (30–100 ng/mL), n=10	0 (0%)	10 (90.9%)	1 (9.1%)
Insufficiency (20–29 ng/mL), n=20	0 (0%)	11 (100%)	0 (0%)
Deficiency (<20 ng/mL), n=69	1 (12.5%)	7 (87.5%)	0 (0%)
M±m, ng/mL	17.30	27.60±1.30	33.1
P value	0.372		
Correlation coefficient	0.21		

P—a probability of difference between the study groups under the Bonferroni-corrected Kruskal-Wallis H test.
*Statistically significant difference in patients with relatively normal VDR levels.
†Statistically significant value of the correlation coefficient (p<0.01).
VDR, vitamin D receptor.

patients with relatively normal VDR levels had erythrocyte sedimentation rate (ESR), RP and IL–6 mean values 16.14±2.49 mm/hour, 8.16±0.54 mg/L and 14.19±1.00 pg/mL, respectively, or in other words, they were 30.7%, 15.7% and 13.1% lower than in patients with low serum VDR levels (p<0.05). Similar patterns were seen while assessing the relationship of VDR with SLEDAI and DI. For example, patients with low VDR concentrations had 18.4% and 27.2% higher corresponding values compared with the patients with relatively normal serum VDR levels (p>0.05). The correlation analysis revealed greater close association of low VDR concentration with elevated CRP (r=−0.22) and IL-6 (r=−0.21) levels, as well as with inflammatory activity index SLEDAI (r=−0.20).

The VDR level was closely associated with serum vitamin D concentration in patients with SLE (table 7). Mean vitamin D concentration in patients with low VDR was 33.55% lower than in the group with relatively normal levels (p=0.0001). Half of the patients with optimal vitamin D value had relatively normal blood serum VDR concentrations, while only 11.6% of the vitamin D deficiency group showed normal VDR readings. Among patients with vitamin D deficiency and insufficiency, the proportion of subjects with low VDR was 48.4% and 20% higher than patients with optimal cholecalciferol supply, respectively. The correlation analysis revealed a moderate positive relationship between the studied indicators (r=0.47).

The mean serum vitamin D concentration in the control group subjects with relatively normal VDR levels was 59.54% higher than in those with low VDR (table 7). However, the differences were not statistically significant (p>0.05), allegedly because of uneven distribution of study subjects in the groups. For practically healthy individuals, a weak positive correlation was spotted between vitamin D concentration and VDR, which nevertheless failed to reach statistical significance (r=0.21; p>0.05).

The analysis of the relationship between blood serum VDR concentrations in patients with SLE and bone turnover markers (table 8) demonstrated a proportional elevation of the bone resorption marker—C-terminal telopeptide of type I collagen (CTX) in line with a decline in VDR value. For example, patients with low VDR concentration had 17.59% higher CTX compared with the group of patients with relatively normal VDR (p<0.05). The close relationship between VDR and CTX was substantiated by the results of correlation analysis (r=−0.27). However, no statistically significant difference was found between OC readings in the groups of patients with low and relatively normal VDR values (p>0.05).

In the next part of our study, we analysed the relationship between VDR level and changes of BMD depending on sex, reproductive function of female subjects and age (table 9). We established no statistically significant difference in the average values of Z-score and BMD in female patients of reproductive age with low and relatively normal blood serum VDR concentrations (p>0.05), although we revealed a clear trend towards decreased values in patients with low VDR. For example, the average value of Z-score in the group of female patients with low

Table 8 Relationship between bone turnover markers (OC, CTX) and blood serum VDR concentration in patients with SLE, M±m

VDR concentration	No.	Bone turnover markers	
		OC, ng/mL n=65	CTX, ng/mL n=65
Low level (<18.28 ng /mL), n=51	1	13.89±0.41	1.27±0.04*
Relatively normal level (18.28–30.73 ng /mL), n=13	2	14.10±1.04	1.08±0.09
High level (>30.73 ng /mL), n=1	3	19.50±0.00	1.02±0.00
P value		0.822	0.038
Correlation coefficient		0.03	−0.27†

P—a probability of the difference between groups 1 and 2 under Mann-Whitney U test in independent samples.
*Statistically significant difference in patients with relatively normal VDR levels.
†Statistically reliable values of the correlation coefficient.
CTX, C-terminal telopeptide of type I collagen; OC, osteocalcin; VDR, vitamin D receptor.

VDR of reproductive age was 3.56 times (LS), 2.33 times (left FN) and 1.94 times (right FN) lower than in the group of patients with relatively normal VDR levels. At the same time, patients with low VDR levels demonstrated BMD 7.07% (LS), 11.11% (left FN) and 7.95% (right FN) lower than that in individuals with relatively normal blood serum VDR. As for postmenopausal female patients, the average T-score for LS in the low-VDR group was 1.57 times lower compared with this indicator in women with relatively normal VDR concentrations, while BMD differed by 4.95% in the same groups of female patients. Although the average FN values of T-score and BMD in the groups of female postmenopausal patients with low and relatively normal VDR levels practically did not differ.

The analysis of a connection between VDR and BMD in male patients with SLE was quite difficult due to the small number of examined subjects. The above may explain the fact that the average value of Z-score in the group of patients under 50 years with a relatively normal VDR level appeared to be 4.65 times (LS), 3.67 times (left FN) and 3 times (right FN) lower than in the group of patients with low VDR concentrations. At the same time, BMD in patients with a relatively normal level of VDR was 26.09% (LS), 24.73% (left FN) and 26.6% (right FN) lower than in individuals with low blood serum VDR concentrations. Male study subjects over 50 years were a group 1.5 times bigger than men of other age groups, which preconditioned the higher statistical value of the results obtained. The mean T-score for LS of male subjects over 50 years with low VDR concentrations was 2.87 times lower than in men with relatively normal VDR levels, while BMD in the same male groups differed by 2.83%. A similar trend was observed while comparing the right FN data. In contrast, the mean T-score and BMD for the left FN were lower in patients with relatively normal VDR levels.

DISCUSSION

The results of the study show that average VDR in patients with SLE was 12.78±0.61 ng/mL, while in the control group this indicator was 1.81 times higher. 77 (77.8%) patients with SLE presented low serum VDR concentrations, while only 22 (22.2%) patients had relatively normal or high values. We used ELISA to measure serum VDR expression in our study subjects. This is an accessible and widely applicable clinical method for systemic assessment of vitamin D signalling pathway status, yet it may not reflect tissue-specific or cellular VDR activity.

According to the study findings, patients with SLE presented reduced VDR mRNA expression.[11–15] For example, De Azevêdo Silva *et al* showed a decrease of VDR expression in patients with SLE compared with controls.[11] According to Luo *et al*, patients with SLE exhibit lower VDR mRNA levels than controls.[13] A recent Chinese study involving 62 patients with SLE also showed reduced VDR mRNA expression and VDR protein concentration in peripheral blood mononuclear cells.[12] Scientists have also found lower VDR expression in patients diagnosed with autoimmune, infectious or oncological diseases, such as rheumatoid arthritis,[23 24] systemic sclerosis,[25] primary biliary cholangitis,[26] tuberculosis,[27] leprosy,[28 29] colon cancer[30] and ovarian cancer.[31]

It is known that regulation of VDR expression is a multifaceted function which greatly depends on environmental influence, and genetic and epigenetic factors.[32] The pathogenetic mechanisms of VDR concentration decrease in patients with SLE remain unclear, but some factors can be assumed to play a role. First of all, a chronic inflammatory process caused by proinflammatory cytokines interferon alpha (IFN-α), IL-6, IL-18, TNF-α and influence of effector cells of the immune system[33] may suppress VDR expression.[12 14 34] Chen *et al* showed that TNF-α induces the expression of microRNA-346 (miR-346) targeting the 3′-untranslated region of VDR mRNA, thus causing the inhibition of VDR protein synthesis.[35] Second, H19 small interfering RNA, miR22-5p and miR675-5p micro-RNAs are able to suppress protein and VDR mRNA expression, contributing to progression of inflammation. This mechanism was investigated in patients with ankylosing spondylitis[36] and ulcerative colitis.[37] And the third, VDR gene polymorphisms may be associated with reduced VDR mRNA expression.[38 39] Moreover, VDR gene single nucleotide polymorphism (SNP), including the most studied

Table 9 Relationship between structural and functional states of bone tissue in women of different reproductive ages and patients with SLE with different VDR levels (M±m)

Indicator		Description	Low level (<18.28 ng/mL) 1	Relatively normal level (18.28–30.73 ng/mL) 2	High level (>30.73 ng/mL) 3	P value
Women of reproductive age			n=27	n=12	n=1	
1	Z-score ≤−2.0 SD	LS	5 (18.52%)	1 (8.33%)	0 (0%)	
		FN (left)	3 (11.11%)	0 (0%)	0 (0%)	
		FN (right)	1 (3.7%)	0 (0%)	0 (0%)	
2	Z-score >−2.0 SD	LS	22 (81.48%)	11 (91.67%)	1 (100%)	
		FN (left)	24 (88.89%)	12 (100%)	1 (100%)	
		FN (right)	26 (96.3%)	12 (100%)	1 (100%)	
3	Z-score, M±m, SD	LS	−0.64±0.25	0.18±0.42	−0.40±0.00	0.10
		FN (left)	−0.56±0.20	0.24±0.38	0.00±0.00	0.08
		FN (right)	−0.33±0.23	0.17±0.31	−0.40±0.00	0.09
4	BMD, g/cm^2	LS	0.99±0.03	1.06±0.04	0.95±0.00	0.12
		FN (left)	0.80±0.03	0.90±0.05	0.80±0.00	0.12
		FN (right)	0.81±0.03	0.88±0.04	0.76±0.00	0.12
Postmenopausal women			n=38	n=6	–	
5	Osteoporosis, T-score −2.5 SD and less	LS	8 (21.05%)	2 (33.33%)	–	
		FN (left)	6 (15.79%)	3 (50%)	–	
		FN (right)	7 (18.42%)	3 (50%)	–	
6	Osteopenia, T-score ranging from −1.0 SD to −2.5 SD	LS	16 (42.11%)	1 (16.67%)	–	
		FN (left)	14 (36.84%)	1 (6.7%)	–	
		FN (right)	14 (36.84%)	0 (0%)	–	
7	Normal, T-score ranging from +2.5 SD to −1.0 SD	LS	14 (36.84%)	3 (50%)	–	
		FN (left)	18 (47.37%)	2 (33.33%)	–	
		FN (right)	17 (44.74%)	3 (50%)	–	
8	T-score, mean, SD	LS	−1.44±0.24	−0.92±0.74	–	0.51
		FN (left)	−1.20±0.24	−1.62±0.66	–	0.45
		FN (right)	−1.25±0.26	−1.45±0.84	–	0.68
9	BMD, g/cm^2	LS	0.96±0.03	1.01±0.07	–	0.43
		FN (left)	0.80±0.03	0.69±0.07	–	0.22
		FN (right)	0.79±0.03	0.77±0.09	–	0.86

P—a probability of difference between groups 1 and 2 by Mann-Whitney U test.
BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; VDR, vitamin D receptor.

ones, such as BsmI (rs1544410), FokI (rs2228570), ApaI (rs7975232) and TaqI (rs731236) may be relevant to SLE risk, disease activity and severity, and the likelihood of emergence of lupus nephritis, but these associations vary depending on subject ethnicity and genotype.[40–43]

In contrast, researchers who have studied the expression of VDR mRNA in CD4+ T cells have reported a significant gain in the proportion of VDR-positive CD4+ T cells, particularly Th1 cells, Treg cells and Tfh cells.[44] It is clear now that immune cells express VDR and CYP27B1 (1α-hydroxylase), indicating that these cells are able to synthesise and respond to the active form of vitamin D.[10] It has been shown that interaction of VDR with ligand in dendritic cells results in a decline of cytokine production, including IL-12 influencing the differentiation of T helpers and Th1 cells, and IL-23 influencing the differentiation of T helpers and Th17 cells, as well as in an increase in the expression of anti-inflammatory cytokine IL-10.[45 46] We also know that T lymphocytes express both VDR and CYP27B1, while naive T lymphocytes express low VDR levels gradually increasing on their activation. The interaction of 1,25-$(OH)_2$-D_3 with VDR inhibits the proliferation and differentiation of CD_4+ T lymphocytes due to the influence of cytokines, for example, Th1 differentiation and secretion of inflammatory cytokines (IL-2, interferon gamma (IFNγ) and TNF-α) are reduced while

Th2 differentiation and secretion of anti-inflammatory cytokines (IL-4, IL-5 and IL-10) are accelerated.[47] The obtained data indicate that VDR activation in T lymphocytes may inhibit the autoimmune aggression.

The analysis of VDR sex differences in patients with SLE did not suggest the statistically significant difference between male and female subjects. A recent study by Peruzzzu *et al* demonstrated a sex-independent effect of calcitriol on VDR expression levels.[48] This finding is consistent with another study that reported equal VDR mRNA expression in men and women.[49]

The highest proportion of low-VDR individuals among the subjects of the main study was recorded in elderly patients (over 60 years). The correlation analysis confirmed the statistically significant relationship between VDR and age of patients with SLE. The literature sources also indicate age-related decline in VDR expression. This conclusion was made after studying rat intestinal and bone cells,[50] as well as human skeletal muscle biopsy samples.[51]

We did not find a relationship between blood serum VDR concentration and disease duration. No evidence of a relationship between VDR concentration and disease duration was found in the available literature. Furthermore, other studies of VDR expression, for example, in patients with multiple sclerosis, have also failed to show any correlation with disease duration.[52]

According to our findings, the highest VDR level was recorded in obese patients, although we did not establish a statistically significant relationship between VDR and BMI in patients with SLE. Other scientists have also reported the elevated expression of VDR mRNA in obese patients compared with individuals with normal BMI.[53–55] We assume this phenomenon is associated with the increased expression of genes encoding cytokines, chemokines and adhesion molecules in adipocytes, thus leading to infiltration of adipose tissue by immune cells and subsequent production of inflammatory mediators. The effect of hsa-miR-125a, hsa-miR-125b-5p and hsa-miR-214–3p microRNAs on regulation of VDR mRNA expression in obese individuals has also been confirmed.[54]

It is known that VDR synthesis is regulated by various hormones, including retinoic acid, parathyroid hormone and GCs.[56] Given that most patients with SLE require long-term GC therapy, we focused on studying the relationship between serum VDR concentration and GC load. The mean VDR concentration in the group of patients with SLE who received a cumulative GC dose ≥35.04 g was 9.01% lower than in the group of patients with GC load <35.04 g ($p>0.05$). The determined correlation coefficient ($r=-0.17$) indicates a weak negative relationship between the studied parameters ($p<0.05$). Unfortunately, no publications about the effect of GC therapy on mRNA level or VDR protein in patients with SLE or other autoimmune diseases have been made so far. We know from the literature that GCs can both increase and decrease VDR expression, depending on the cell type. For example, the study on GC regulation of VDR synthesis and activity in squamous cell carcinoma cells by Hidalgo *et al* showed that dexamethasone contributed to elevation of VDR protein concentration and enhanced its binding to the ligand.[57 58] In contrast, dexamethasone reduced VDR mRNA levels in human osteosarcoma cells, apparently by inhibiting VDR gene transcription or influence on VDR mRNA processing.[59]

Analysis of the relationship between blood serum VDR and a diagnosis of lupus nephritis showed that patients with kidney damage had an 8.2% higher proportion of low-VDR individuals than those without a nephritis diagnosis. The average concentration of the studied matter in the group of patients not diagnosed with lupus nephritis was approximately 4% higher compared with the group of patients with impaired renal function ($p>0.05$). The observed trend is consistent with the results of other studies. For example, De Azevêdo Silva *et al* confirmed a more significant decrease of VDR expression in patients diagnosed with lupus nephritis compared with patients with SLE without renal impairment.[11] In another study, Sun *et al* used immunohistochemistry assay to examine VDR expression in kidney tissue samples taken from patients diagnosed with lupus nephritis. The scientists found that VDR expression in the patient group was lower than in the control group and negatively correlated with SLICC kidney activity index.[60]

An important pathogenetic factor of an adverse effect on regulation of VDR expression in patients with SLE is considered a systemic inflammatory process. Specifically, a decrease in blood serum VDR concentration in patients with SLE was associated with elevated ESR, CRP and IL-6 indicators. For example, patients with low VDR demonstrated 44.3%, 18.6% and 15.1% higher mean values of ESR, CRP and IL-6 than patients with relatively normal serum VDR levels, respectively ($p<0.05$). In addition, the low-VDR patient group had SLEDAI-2 K and SLICC/ACR DI indices 18.4% and 27.2% higher than patients with SLE with relatively normal blood serum VDR levels, accordingly ($p>0.05$). The results of the correlation analysis clearly showed that low VDR readings were more closely associated with elevated levels of CRP ($r=-0.22$) and IL-6 ($r=-0.21$), as well as with the inflammatory process activity index SLEDAI-2K ($r=-0.20$). Some studies reported the existence of a connection between VDR expression and markers of inflammatory activity. Recently, Chinese researchers studied VDR expression in peripheral blood mononuclear cells of 95 patients with SLE and found a negative correlation of VDR mRNA levels with SLEDAI-2K, TNF-α and IL-6 readings.[14] This finding is consistent with the results of another Chinese study that showed that VDR mRNA and protein expression in peripheral blood mononuclear cells was significantly lower in patients with SLE than in controls and negatively correlated with SLEDAI.[16]

According to the literature, the VDR gene itself is considered one of the genomic targets for vitamin D. This type of regulation has been studied in various cell culture models, including 3T6 mouse fibroblasts,[61] human HL-60

cells[62] and MG-63 osteosarcoma cells,[63] and identified in in vivo vitamin D target tissues.[64–67] The study by Zella *et al* allowed to establish several enhancers in two separate introns of the VDR gene responsible for autoregulation of transcription mediated by vitamin D.[68 69] A post-translational VDR regulation mediated by vitamin D responsible for better stability of VDR protein interacted with a ligand also exists.[70] Therefore, the insufficiency or deficiency of vitamin D naturally leads to a decrease in VDR concentration because of suppressed transcription of the corresponding gene. The close direct relationship between VDR concentration and supply of vitamin D in patients with SLE was also confirmed by the results of our study. For example, the average vitamin D value in patients with low VDR was 33.55% lower than in the group with a relatively normal level (p=0.0001). The proportion of individuals with low VDR among patients with vitamin D deficiency and insufficiency was 48.4% and 20% higher than in patients with optimal vitamin D supply, respectively.

In the next section of our work, we analysed the relationship between VDR protein content and bone turnover markers such as CTX, OC and BMD measured by DXA. We established that the elevation of the bone resorption marker CTX was proportional to the decrease in VDR value. For example, patients with low VDR had 17.59% higher CTX than the group of patients with relatively normal VDR levels (p<0.05). At the same time, no statistically significant difference was found in the concentration of OC in the groups of patients with low and relatively normal VDR values. Data from scientific sources on the relationship between VDR mRNA, protein expression and bone turnover markers are very limited. One of the few studies on this topic was conducted by Australian scientists Ormsby *et al*, who studied the effect of vitamin D metabolism gene expression on bone remodelling showing the association of VDR mRNA expression with genes that control the resorption processes.[71]

As for structural changes of bone tissue, no statistically significant difference was found between the groups of patients with SLE with low and relatively normal levels of VDR in terms of mean values of Z-scores and T-scores, as well as BMD. Obvious differences were observed only between groups of patients of reproductive age. For example, patients of reproductive age with low VDR levels had mean Z-score values 3.56 times (LS), 2.33 times (left FN) and 1.94 times (right FN) lower than the patients with relatively normal VDR levels. At the same time, BMD differed by 7.07% (LS), 11.11% (left FN) and 7.95% (right FN) in the same groups of study participants. Postmenopausal female subjects showed a similar trend regarding the corresponding LS indicators. Establishing a relationship between VDR and BMD in male patients with SLE was somewhat complicated due to the small number of study subjects. In general, the assumption of the effect of VDR gene alleles on BMD emerged more than 30 years ago.[72] Currently, scientists explain the relationship between the VDR mRNA level and the structural state of bone tissue by polymorphisms of the VDR gene. Specifically, a meta-analysis of 14 observational studies conducted by Pakpahan *et al* revealed that BsmI and FokI polymorphisms of the VDR gene correlated with decreased BMD in male subjects.[73] We found only one study conducted in China among the available literature sources that examined the relationship between vitamin D status, VDR gene expression and BMD in patients with early stage SLE. According to its results, Zheng *et al* reported no difference in VDR gene expression between groups of patients with osteopenia and normal BMD, and absence of correlation between VDR mRNA and BMD readings.[74]

Our study had several limitations. First, it was conducted with only a single measurement of blood serum VDR concentration. We used the ELISA test for determining the VDR protein and did not compare the obtained data with the survey of VDR mRNA expression using PCR. Second, the main group of the study consisted mostly of patients with high activity of the inflammatory process. Third, the small number of male patients with SLE in the study sample made it difficult to perform statistical calculations and did not allow ensuring the reliability of the obtained data. Fourth, this study did not take into account polymorphisms of the VDR gene able to influence VDR expression, change the sensitivity of receptors to vitamin D and, accordingly, to exert effect on the disease course and bone metabolism. Studying the associations between SNP variants of the VDR gene and vitamin D concentrations, VDR expression, clinical manifestations and status of bone tissue in patients with SLE is a promising direction for further research, which will allow for a deeper understanding of the pathogenetic mechanisms and contribute to improving the approach to management of this group of patients.

The advantage of the study is its multifactorial nature. We investigated the role of the disease course factors and the activity of the inflammatory process in shaping the VDR status, as well as its relationship with bone turnover markers and BMD changes assessed by DXA. The results obtained deepen the understanding of the pathogenetic mechanisms influencing vitamin D and VDR status in patients with SLE and indicate the potential role of VDR expression level as an additional marker of inflammatory activity and bone resorption. Application of these data in clinical practice is an important issue in terms of personalised hypovitaminosis D correction aimed at reducing disease activity and preventing osteoporosis.

CONCLUSIONS

Now, summarising the obtained results, we can clearly formulate that low VDR blood serum concentration (below 18.28 ng/mL) is quite common in patients with SLE. 77 (77.8%) patients with SLE had low VDR readings, while only 22 (22.2%) patients had relatively normal or high levels. Low serum VDR concentration was associated with ageing patients, high activity of inflammatory

processes (ESR, CRP, IL-6, SLEDAI-2K), hypovitaminosis D and bone resorption marker (CTX). VDR status had no statistically significant association with sex, disease duration, cumulative GC dose, BMI, a diagnosis of lupus nephritis, disease severity (SLICC/ACR DI), bone formation marker (OC) and BMD readings.

Contributors SS was responsible for the study design, data collection, statistical analysis and final approval of the article. TM was responsible for the literature review, patients selection, conducting the study, statistical analysis and manuscript writing. LM assisted with data collection and statistical analysis. LD contributed to the literature review and analysis of the study results. SS is the guarantor of the overall content. All authors contributed to the manuscript and approved the submitted version. AI tools (eg, ChatGPT) were used solely for language enhancement, such as improving sentence clarity, selecting appropriate synonyms and polishing grammar. No AI-generated content was used for scientific interpretation, data analysis or original text writing. All scientific conclusions, analyses and interpretations were conducted and written by the authors.

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