Reverse Relationship of Uric Acid and Vitamin D3 in Adult Patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus

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Background: The relationship between uric acid (UA) and vitamin D3 (25(OH)D) in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients has not been settled yet.

Objective: To evaluate a possible link between UA and 25(OH)D serum levels and vitamin D3 therapy in patients with RA compared to SLE.

Design: A Retrospective Study.

Setting: Salmaniya Medical Complex, Ministry of Health, Bahrain.

Method: Eighty patients with RA and SLE from March 2015 to September 2018 were included in the study. Serum level of UA and 25(OH) D levels were estimated before and after oral vitamin D3 therapy. Data were analyzed using SPSS version 19.

Result: RA and SLE had a significant increase in mean serum 25(OH)D, (P=0.0001) after vitamin D3 therapy, but a decreased mean serum UA (P=0.0001). The increase in 25(OH)D was more prominent in SLE (P=0.0001) compared to RA (P=0.002), while the decrease in serum UA after vitamin D3 therapy was more prominent in RA (P=0.0001) compared to SLE (P=0.048).

Conclusion: We found an inverse relation between serum 25(OH)D and UA in adult Bahraini patients with RA and SLE, which was more pronounced in RA compared to SLE patients.

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The association between gout and autoimmune rheumatic diseases has rarely been reported. In RA, a negative association with gout has been widely established. Gout does occur in patients with RA; however, at a lower rate than in the general population[1]. RA was found to be the most significant co-morbidity associated with carpal tunnel syndrome (CTS), followed by gout[2]. On the other hand, gout in SLE has been reported to be rare as only a few sporadic cases have been reported from 1985 to 2000; however, after the year 2000, concomitant gout and SLE were also studied[3].

Vitamin D has widely been associated with autoimmune systemic diseases such as type 1 diabetes mellitus (DM) and multiple sclerosis (MS); however, in autoimmune rheumatic diseases, reports were controversial[4]. In 2003, Rossini et al stated that there was no conclusive evidence of the efficacy of a preventive or therapeutic strategy based on vitamin D supplementation and that vitamin D intake was not associated with risk of SLE or RA in females[5]. A study reported that vitamin D deficiency does not increase the risk of RA[6]. It has been reported that vitamin D deficiency is highly prevalent in patients with RA and it may be linked to disease severity and diffuse musculoskeletal pain in RA[7].

Coexistence of gout and SLE is rarely reported due to the possibility that SLE prevents the expression of gout or vice-versa. Gout should be considered in the differential diagnosis of patients with SLE who present with acute arthritis[8]. Increased serum UA level is associated with pulmonary arterial hypertension (PAH) in SLE patients[9]. In addition, it could be

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used as a marker for screening[10]. A study revealed that higher UA levels contribute to renal damage in SLE patients[11].

An association has been reported between serum VD and UA concentrations, and their interaction with disease activity in rheumatic diseases in general and RA and SLE in particular[6]. One study suggested that serum UA may directly decrease serum VD in patients with gout by inhibiting 1-alpha-hydroxylase activity[12]. It has been reported recently that VD levels are more important than UA in regulating bone mineral density (BMD) in patients with chronic kidney disease[13]. The latter hypothesis was contradicted by evidence that found positive associations of UA with vitamin D related phenotypes such as BMD and dementia[14,15]. Recently, it was found that allopurinol is effective in lowering hyperuricemia and treating hypovitaminosis[16]. In addition, a study revealed that insufficiency in serum VD was significantly associated with elevated UA in middle-aged and elderly women[17]. However, in patients with RA concomitant occurrence of gout and VD deficiency is lacking in the literature. However, in SLE patients concomitant occurrence of gout and VD deficiency has been reported occasionally; although, the relation between these two factors is still debatable.

The aim of this study is to evaluate a possible link between UA and 25(OH)D serum levels and vitamin D3 therapy in patients with RA compared to SLE.

METHOD

Eighty Bahraini patients above 12 years old diagnosed with RA or SLE between March 2015 and September 2018 were included in the study; 30 had RA and 50 had SLE. All patients had serum UA and vitamin D (25(OH)D) tested before and after vitamin D3 therapy. Measurement of the serum level VD was performed using Chemiluminescence immunoassay on Advia Centaur Analyzer (LoD 8.0 nmol/L). VD deficiency was defined as < 30 nmol/L, insufficiency was defined as 30-49 nmol/l, and optimal level was defined as ≥ 50nmol/L. Measurement of the serum level of UA was performed using uricase (enzymatic) method. Reference range of serum UA was defined 220–547 for males and 184–464 micromol/L for females. Patients who did not have UA and vitamin D levels tested at the same time were excluded.

SPSS version 19 was used to analyze the data. Results were cross-tabulated to examine the independence between variables. Statistics were performed using Pearson correlation and Analysis of Variance (ANOVA) as appropriate. A P-value of ≤ 0.05 was considered as statistically significant.

RESULT

Eighty patients were included in this study. The mean age of the patients was 45.21 years (range 16–77 years, SD=14.82). Seventy (87.5%) patients were females (SLE=44 and RA=26) and 10 were males (SLE=6 and RA=4). Fifty (62.5%) patients had SLE, their mean age was 39.16 years (range 16-61 years, SD=14.12). Thirty (37.5%) patients had RA, their mean age was 55.3 years (range 38 -77 years, SD=9.65). Nineteen (23.75%) patients were deficient, 34 (42.5%) were insufficient, and 27 (33.75%) were optimal. After vitamin D therapy, 69 (86.3%) patients achieved optimal levels, 10 (12.5%) had insufficient levels and one (1.25%) was deficient.

The mean serum level of VD was significantly increased after VD therapy from 47.59 nmol/l to 78.52 nmol/l with an increment in the mean serum levels of 30.92 nmol/l and the difference was statistically significant (P=0.0001). On the other hand, the mean serum level of UA in our cohort was significantly decreased from baseline after VD therapy (335.38 micromol/L to 303.98 micromol/L; the difference was statistically significant (P=0.0001), see table 1.

Table 1: Reverse Relationship of UA and Vitamin D3 in Patients with Two-Related Rheumatic Diseases

	Paired Differences						Sig (2tail)			
	Mean diff	Mean	Std. Dev	Std. EM	95% C I Lower	95% C I Upper		N	Correlation	Sig.
VD1 -VD2	-30.92	47.59-78.51	31.04	3.47	-37.83	-24.02	0.0001	80	0.556	0.0001
UA1 - UA2	31.40	335.38 - 303.98	74.98	8.38	14.72	48.08	0.0001	80	0.808	0.0001

SLE= Systemic lupus erythematosus, RA=Rheumatoid arthritis. VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline, UA2= Uric Acid after vitamin D therapy.

In SLE patients, the mean serum level of VD increased after VD therapy from 39.15 nmol/l to 73.41 nmol/l (P=0.0001). The mean serum level of UA decreased after VD therapy from 351.90 micromol/L to 329.82 micromol/L, and that was statistically significant (P=0.048), see table 2.

Table 2: Increased Vitamin D3 and Decreased Uric Acid Serum Levels in Patients with SLE

Disease = SLE	Paired Differences						Sig. (2-tail)			
	Mean diff	MEAN	Std. Dev	Std. E Mean	95% C I Lower	95% C I Upper		N	Corre.	Sig.
VD1 - VD2	-34.25	39.15-73.41	22.24	3.14	-0.58	-27.93	0.0001	50	0.31	0.02
UA1 - UA2	22.08	351.90-329.82	76.86	10.87	.2354	43.92	0.048	50	0.831	0.001

VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline, UA2= Uric Acid after vitamin D therapy, SLE= systemic lupus erythematosus.

In RA patients, the mean serum VD level increased after VD therapy from 61.67 nmol/l to 87.03 nmol/l (P=0.002), while the mean serum UA decreased after VD therapy from 307.83 micromol/L to 260.90 micromol/L and that was statistically significant (P=0.001), see table 3.

Table 3: Decreased Uric Acid and Increased Vitamin D3 Levels in Patients with RA

Disease = RA	Paired Differences						Sig (2tail)			
	Mean Diff	Mean	Std. Deviation	Std. EM	95% C I Lower	95% C I Upper		N	Correlation	Sig.
VD1 - VD2	-25.36	61.66-87.03	41.68	7.60	-40.93	-9.80	0.002	30	.605	0.001
UA1 - UA2	46.93	307.83-260.90	70.22	12.82	20.71	73.15	0.001	30	.701	0.001

VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline, UA2= Uric Acid after vitamin D therapy, RA=rheumatoid arthritis.

The SLE patients had statistically significant lower serum levels of 25(OH)D at baseline (VD1) compared to RA patients (P=0.0001), but no difference between the two groups after therapy. Conversely, RA patients had statistically significant lower serum levels of UA after vitamin D3 therapy compared to SLE patients (P=0.015), but no difference between the groups at baseline levels.

Table 4: Comparison between Mean Serum UA in SLE and RA after VD Therapy

		N	Mean	Std. Dev	Std. Error	95% C I		Sig.
						Lower	Upper	
VD1	SLE	50	39.15	12.82	1.81	35.51	42.79	0.001
	RA	30	61.66	33.07	6.03	49.32	74.02	
	Total	80	47.59	24.97	2.79	42.04	53.15	
VD2	SLE	50	73.41	22.64	3.20	66.97	79.84	0.11
	RA	30	87.03	52.31	9.55	67.49	106.57	
	Total	80	78.51	36.96	4.13	70.29	86.75	
UA1	SLE	50	351.90	132.73	18.77	314.18	389.62	0.10
	RA	30	307.83	79.83	14.57	278.02	337.64	
	Total	80	335.37	117.17	13.10	309.29	361.45	
UA2	SLE	50	329.82	131.87	18.65	292.34	367.29	0.01
	RA	30	260.90	97.00	17.71	224.67	297.12	
	Total	80	303.97	123.96	13.86	276.38	331.56	

VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline,
UA2= Uric Acid after therapy,
SLE=Systemic lupus erythematosus,
RA= Rheumatoid arthritis.

Twenty-five patients were <40 years, the mean was 26 years, range 16-38 years (4 were males and 21 were females). Fifty-five patients were ≥40 years, with a mean age of 52.9 and range of 41-77 years (6 were males and 49 were females), see table 5. Patients aged <40 years had lower mean serum levels VD at baseline (VD1) compared to those >40 years and the difference was statistically significant (P=0.013). No difference was found between the groups after vitamin D therapy (VD2).

Table 5: Comparison between Patients before and after Vitamin D3 Therapy

	Age	N	Mean	Std. Dev	Std. Error	C I 95%		P-value
						Lower	Upper	
VD1	15-40	25	37.40	14.75	2.95	31.30	43.49	0.01
	41-78	55	52.22	27.31	3.68	44.84	59.61	
	Total	80	47.59	24.97	2.79	42.03	53.15	
VD2	15-40	25	71.34	21.34	4.26	62.53	80.14	0.24
	41-78	55	81.78	41.98	5.66	70.43	93.13	
	Total	80	78.51	36.96	4.13	70.29	86.74	
UA1	15-40	25	384.72	156.63	31.32	320.06	449.37	0.01
	41-78	55	312.94	86.84	11.70	289.46	336.42	
	Total	80	335.37	117.17	13.10	309.29	361.45	
UA2	15-40	25	342.52	151.66	30.33	279.91	405.12	0.06
	41-78	55	286.45	106.11	14.30	257.76	315.14	
	Total	80	303.97	123.96	13.86	276.38	331.56	

VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline, UA2= Uric Acid after therapy.

Patients >40 years had lower mean serum level of UA both at baseline (UA1) and after vitamin D therapy compared to those <40 and the difference was statistically significant only at baseline (P=0.010 and P=0.060, respectively). No statistical difference was found between males and females in serum levels of VD or uric acid.

Significant increase in VD and decrease in UA in both age groups was found; P=0.06 and P=0.001, respectively, in those <40 years and P=0.001 and P=0.001, respectively, in those >40 years.

Table 6: Reduction of Serum UA in Response to Vitamin D Therapy in Age Groups; Less and More than 40 Years

	Paired Differences						Sig. (2-tail)			
	Mean Diff	MEAN	Std. Dev	Std. E Mean	95% C I			N	Corre	Sig.
					Lower	Upper				
Age Groups (15-40)										
VD1 - VD2	-33.94	37.40-71.34	20.83	4.16	-42.53	-25.34	0.0001	25	0.38	0.06
UA1 - UA2	42.20	384.72-342.52	49.09	9.81	21.93	62.46	0.0001	25	0.95	0.001
Age Groups (41-78)										
VD1 - VD2	-29.55	52.22- 81.78	34.79	4.69	-38.95	-20.14	0.0001	55	0.56	0.0001
UA1 - UA2	26.49	312.94- 286.45	84.10	11.34	3.75	49.22	0.023	55	0.63	0.0001

VD1= Vitamin D at baseline, VD2= Vitamin D after therapy; UA1= Uric acid at baseline, UA2= Uric Acid after therapy.

DISCUSSION

The possible link between UA, VD, SLE or RA and their association with autoimmune rheumatic diseases has not been settled yet. We have previously described VD status in Bahraini patients with SLE[18]. The relation between these two factors in RA patients compared to SLE patients has not been examined before. Clinical improvement was found after VD therapy in patients with SLE in some studies[19].

In our study, we found that 23.7% of the patients were deficient, 66.2% had abnormal VD levels, and 33.7% had optimal VD levels. These results were not consistent with our previous study on SLE patients where more than 95% were deficient in VD[18]. After VD therapy, we found that only one patient had VD deficiency, but 12.5% of patients had insufficient levels and 86.25% achieved optimal VD levels. Some of our patients had insufficient levels, which could be due to the second blood sample taken three months before (therapeutic period) or drug non-compliance. Only 3 patients had VD levels >150 nmol/l, but 2 of them had baseline levels >100 nmol/l and no hypercalcemia was recorded. The lower the baseline of vitamin D3 levels, the higher the increment in its serum levels[20]. On the other hand, our RA patients showed more reduction in serum UA after vitamin D3 therapy compared to SLE patients.

Our findings were consistent with another study, which revealed that hyperuricemia can suppress 1-α-hydroxylase and lead to decreasing VD concentration[21]. VD supplementation is needed for patients with renal involvement[22]. UA level could be associated with the development of lupus nephritis in SLE patients[23].

Our results of hyperuricemia with low vitamin D in RA could be compared with previous findings of associated metabolic syndrome and dyslipidemia in rheumatoid arthritis[24]. The

published data of the lack of association between vitamin D levels at baseline with RA, inflammatory markers and response to non-biological therapy could be due to hyperuricemia and the need for correction of hypovitaminosis[25]. Our findings should be confirmed with other prospective cohort studies.

Our study had some limitations due to its retrospective nature. In addition, VD levels were measured at only two-time points (longitudinal). The second sample in some patients was not taken at the end of the therapeutic period (three months). In addition, our cohort was small. Unavailability of data on dietary intake of VD containing foods and medications could be considered as other important limitations.

CONCLUSION

Our study showed a strong inverse correlation between serum UA and serum VD in RA and SLE diseases. Therefore, therapy of hypovitaminosis D in patients with RA and SLE diseases could improve the level of serum UA. The study revealed that vitamin D deficiency was associated with both SLE patients and younger age groups, while RA patients and older age groups associated with lower serum UA at baseline. We recommend vitamin D3 therapy for Bahraini patients with rheumatic diseases as this may induce clinical improvement.

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