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ORIGINAL ARTICLE

Decreased Uric Acid and Phosphorus Levels in Active Juvenile Systemic Lupus Erythematosus

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Abstract

Introduction: The aim of the present study was to investigate serum phosphate and uric acid levels (UA) in juvenile systemic lupus erythematosus (jSLE) and to ascertain their relationship, if any, with disease activity and lupus nephritis.

Methods: Included in the study were 18 children with jSLE who were investigated retrospectively during the active phase (AP) and remission phase (RP) of jSLE.

Results: Serum phosphate and UA levels were found to be significantly lower in AP than in the RP (2.5±0.3/4.2±0.08 mg/dL, p=0.0001 and 2.9±0.3/5±0.2 mg/dL, p=0.0001, respectively). Serum phosphate levels were strongly correlated with serum albumin levels (r=0.772, p=0.0001) and platelet count (r=0.735, p=0.001) and negative associated with D-dimer (r=−0.750, p=0.0001) in AP. No correlation was identified between serum phosphate and UA or creatinine levels in patients with AP, while serum phosphate and UA levels were similar in children with and without nephritis (p>0.05). Serum phosphate levels were correlated with platelet count and UA levels and were inversely related with D-dimer levels in jSLE patients with nephritis (p<0.05).

Discussion and Conclusion: Serum phosphate and UA levels can reflect the activation and low serum levels may be useful biomarkers for the detection of AP in jSLE patients with and without nephritis.

Keywords: Childhood; hypophosphatemia; hypouricemia; juvenile systemic lupus erythematosus; nephritis.

Juvenile systemic lupus erythematosus (jSLE) is a chronic inflammatory disease that affects many systems in the body, although its etiology is unknown. It is characterized by circulating self-reactive antibodies that deposit in tissues and organs[1]. jSLE also affects laboratory findings, such as blood leukocyte and thrombocyte counts; erythrocyte sedimentation rate (ESR); and hemoglobin, complement, creatinine, C-reactive protein (CRP), and Vitamin D levels[2-4]. Data on the role of autoantibodies and inflammation in jSLE are increasing[5]. On the other hand, studies of electrolyte abnormalities, including phosphate and uric acid (UA), are limited in literature in SLE. UA is a catabolite of the purines derived from DNA and RNA, and has been identified as an endogenous adjuvant that drives immune response[6]. The overproduction of UA has been proven to play an emerging role in human diseases such as cardiovascular disease and gout. On the other hand, low serum UA levels might be related with some autoimmune diseases[7]. Moreover, in some studies, low serum UA level has been shown due to the use of UA in inflammatory conditions[8,9].

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Phosphate plays a key role in several biological processes, regulating gene transcription, enzyme activation, bone-kidney-intestine interaction, etc[10]. Although hyperphosphatemia is common, especially in kidney diseases, low serum phosphate is a rare condition. Hypophosphatemia may be seen in neurologic, cardiopulmonary, musculoskeletal, hematological, and metabolic dysfunctions[11,12]. Da Chunha et al.[13] suggested that hypophosphatemia is probably secondary to rapid shifts of extracellular phosphate into the intracellular compartment as an acute-phase response in inflammatory diseases.

In this retrospective study, we investigate the relationship between phosphate and uric acid levels in the active phase (AP) and remission phase (RP) of jSLE in the same patients. Acute-phase reactants (albumin, CRP, fibrinogen, and ESR) and other laboratory parameters (serum anti-dsDNA, creatinine, D-Dimer, thrombocyte counts, urine protein/creatinine ratio, and complements C3 and C4) were also evaluated in patients with or without lupus nephritis.

Materials and Methods

The data of children with jSLE who presented to our pediatric nephrology department were analyzed retrospectively over a 6-year period. This study was reviewed and approved by Ethics Committee (This study was reviewed and approved by Ethics Committee (Düzce University Ethic Committee, Report number: 2021/18). Written informed consent of the families was obtained. All patients were diagnosed with jSLE based on the American College of Rheumatology criteria[14]. At the time of diagnosis, clinical findings and biochemical parameters were used for the SLE disease activity scores. Patients with mild (new-onset low-grade fevers, malar rash, arthralgia, and increasing fatigue), moderate (pleuritic chest pain or pleurisy, swollen elbow, and elevation of the acute-phase reactants), and severe (new onset renal insufficiency, significant proteinuria due to lupus nephritis, decreased complement C3 and C4 levels, elevated anti-dsDNA, and acute-phase reactants levels) flares of jSLE were defined as being at the AP of the disease[5]. Complete absence of clinical disease activity, normal acute-phase reactant levels, and normocomplementemic for the past 1 year was defined as remission. On the other hand, activity categories have been also defined based on SLEDAI score (no activity [SLEDAI = 0], mild activity [SLEDAI = 1–5], moderate activity [SLEDAI= 6–10], high activity [SLEDAI= 11–19], and very high activity [SLEDAI ≥20])[15]. Blood samples were obtained in the morning and serum biochemistry was performed using routine laboratory techniques on jSLE patients in the AP and RP. Antinuclear antibody was measured using indirect immunofluorescence method and anti-dsDNA levels were measured using an ELISA kit.

Renal biopsies were performed on patients who have an acute increase in serum creatinine, proteinuria, hematuria in the presence of any level of proteinuria, and active sediment/cellular casts, and were evaluated based on ACR criteria. Of the total sample, eight patients had lupus nephritis, and all cases with lupus nephritis ISN Class IV or Class III were treated with intravenous methylprednisolone and monthly intravenous cyclophosphamide, with maintenance therapy of mycophenolate mofetil and oral prednisolone. Of the total, 16 (88.8%) patients were also treated with hydroxychloroquine. Patients who used intestinal phosphate-binding drugs and those with elevated parathyroid hormone (PTH) levels, systemic or local infection, or metabolic disease were excluded from the study.

Statistical analysis was performed using SPSS for Windows (Version 11.0. Chicago, SPSS Inc.). All values were stated as the mean±SD. Mean values were compared with a Mann–Whitney U and t tests. Pearson's and Spearman's rho correlation tests were used to identify the relationship between the measured and assayed parameters. $P<0.05$ was accepted as statistically significant.

Results

Included in the present study were 18 jSLE patients (1 male [5.5%]; 17 female [94.5%]), whose clinical features are summarized in Table 1. Arthritis was the most common symptom (Table 1). Biopsy-proven jSLE nephritis was identified in eight of the 18 patients. The WHO Class IV nephritis was identified in 5 (27.7%) patients; 2 patients (11.1%) exhibited typical FSGS lesions on renal biopsy; and only 1 (5.5%) patient had Class V nephritis.

The antinuclear antibody positivity ratio was 88.9% while anti-dsDNA (anti-double-stranded DNA) positivity ratio was 61% (Table 1). Lupus anticoagulants positivity was found in 10 (55.6%) patients; and 5 patients (29.4%) had positive ANCA immunofluorescence test. The biochemical findings in AP and RP are presented in Table 2. SLEDAI score was 15.3±5.7 in patients with AP. Serum phosphate and UA levels were significantly lower in AP than in RP (2.5±0.3 vs. 4.2±0.08 mg/dL, p=0.0001 and 2.9±0.3 vs. 5±0.2 mg/dL, p=0.0001, respectively) (Fig. 1a, b). On the other hand, serum phosphate levels were strongly correlated with serum albumin levels (r=0.772, p=0.0001) and platelet count (r=0.735, p=0.001) in AP (Table 3), and were also strongly negatively correlated with D-dimer levels (r=–0.750, p=0.0001). Serum

Table 1. Clinical and laboratory features of the patients (n=18)

Sex (girls/boys; n)	17/1
Age (years)	14±2.65
	(n/%)
Symptoms	
Arthritis	15 (83.3)
Fever	4 (22.2)
Aphthous ulceration	7 (38.9)
Malar rash	11 (61.1)
Photosensitivity	9 (50)
Pericarditis	3 (16.6)
Central nervous involvement	1 (6.25)
Pleural effusion	4 (22.2)
	(n/%)
Laboratory	
ANA positivity	16 (88.9)
Elevated anti-dsDNA	11 (61)
Lupus anticoagulants antibodies positivity	10 (55.6)
Anti-RNP positivity	5 (27.7)
Anti-Smith positivity	4 (22.2)
ANCA positivity	4 (22.2)
Low complement C3	13 (72.2)
Low complement C4	11 (61)
C-reactive protein positivity	9 (50)
Elevated ESR (>30 mm/h)	13 (72.2)

ANA: Anti-nuclear antibody; dsDNA: Double-stranded DNA; ANCA: Antineutrophilic cytoplasmic antibody; RNP: Ribonucleoprotein particle; ESR: Erythrocyte sedimentation rate.

UA levels were weakly correlated with platelet counts and inversely correlated with D-dimer levels (r=0.513, p=0.029 and r=−0.584, p=0.011, respectively, [Table 3]). There was a weak correlation between serum phosphate and UA levels in AP (r=0.558, p=0.016).

Serum anti-dsDNA levels were found not to be associated with such acute-phase markers as CRP, D-dimer, fibrinogen, creatinine, and spot urine protein/creatinine ratio (p>0.05), while anti-dsDNA levels were correlated with ESR (ESR: r=0.628, p=0.005).

Patients were also divided into groups according to severe hypophosphatemia and hypouricemia. Of the total, six patients developed marked hypouricemia (<2 mg/dL), and eight patients developed marked hypophosphatemia (<2.5 mg/dL) during AP, and all those with marked hypophosphatemia also had concurrent hypouricemia. Serum complement C3, albumin levels, and blood platelet counts were decreased significantly in children who developed marked hypophosphatemia (Table 4), and serum creatinine, D-dimer levels, and ESR were high in these patients (Table 4). There was an inverse correlation with phosphate levels and D-dimer in patients with marked hypophosphatemia (r=−0.756, p=0.030) (Fig. 2). It should be noted that two patients with marked hypophosphatemia were found to be resistant to immunosuppressive treatment, and these patients were treated successfully with eculizumab and rituximab.

Platelet count was decreased statistically significant in the patients who developed marked hypouricemia (Table 4). Although serum D-Dimer level was high, serum albumin levels and platelet count were low in these patients (Table 4). An inverse correlation with UA levels and CRP was noted (r=−0.837, p=0.038) (Fig. 3).

Eight patients had biopsy proven nephritis. The laboratory findings of patients with and without nephritis are presented in Table 5. Notably, 6 of the 8 (75%) patients with marked hypophosphatemia had nephritis. Serum phos-

Table 2. Biochemical findings of the patients

	Active stage (Mean±SEM)	**Remission stage (Mean±SEM)**	**p**
Anti-double-stranded DNA (U/mL)	4.21±1.16	1.3±0.5	0.001
C-reactive protein (mg/dL)	7.0±2.28	0.3±0.02	0.006
Complement C3 (mg/dL)	66.4±8.7	114.9±5.71	0.0001
Fibrinogen (mg/dL)	461.2±38.6	252.4±16	0.0001
Hemoglobin (g/dL)	10.1±0.77	13.5±0.3	0.001
Platelet count (mm^3)	149.944.4±20.137.5	301.222.2±15.249.5	0.0001
Erythrocyte sedimentation rate (mm/h)	71.4±9.45	9.7±2.3	0.0001
Creatinine (mg/dL)	1.34±0.34	0.42±0.03	0.0001
Albumin (gr/dL)	3.21±0.22	4.47±0.12	0.0001
D-dimer (mg/L)	10.07±2.51	1.53±0.4	0.004
Urine protein/creatinine ratio	0.99±0.34	0.42±0.03	0.016

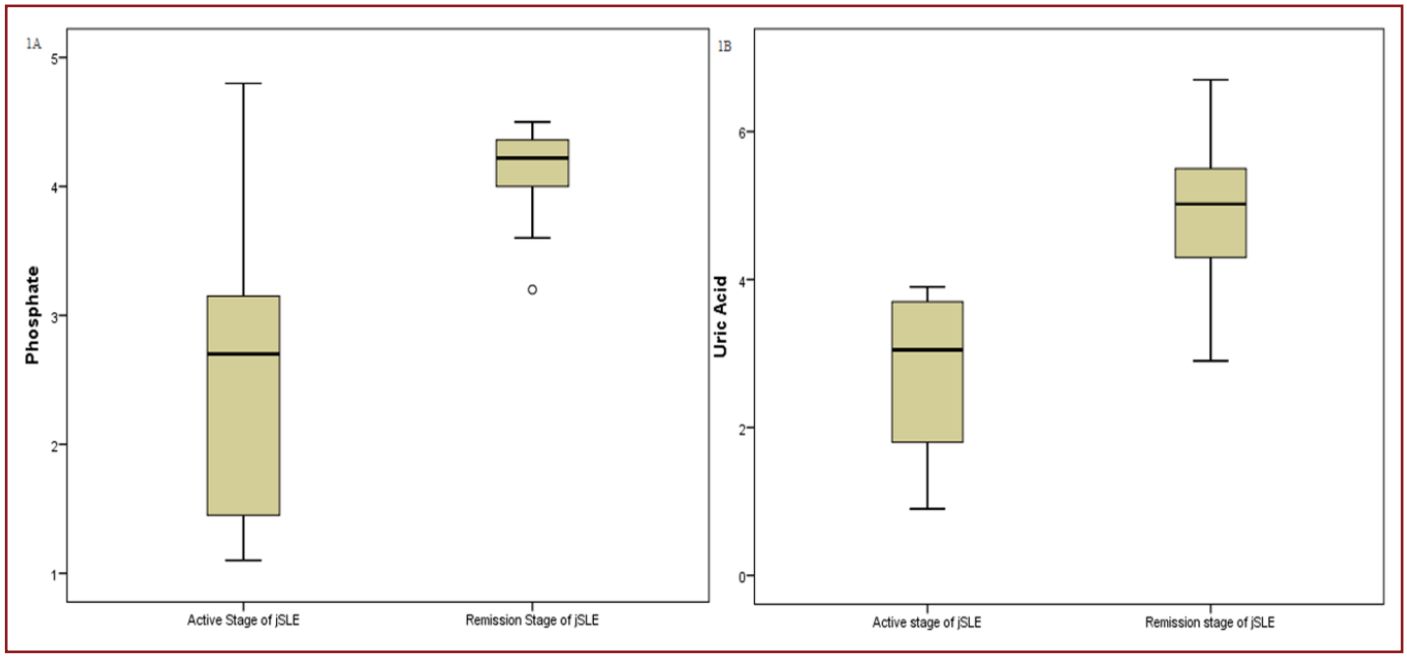

Figure 1. (a, b) The serum phosphate and uric acid levels in AS and RS.

Table 3. Correlations between serum phosphate or uric acid levels and other parameters in children with active stage of juvenile systemic lupus erythematosus

	Phosphate		Uric acid	
	r	p	r	p
Albumin (gr/dL)	0.772	0.0001	0.293	>0.05
Platelet count (mm^3)	0.735	0.001	0.513	0.029
D-dimer (mg/L)	–0.750	0.0001	–0.584	0.011
Phosphate (mg/dL)		-	0.558	0.016
Uric acid (mg/dL)	0.558	0.016		

phate and UA levels were similar in patients with and without lupus nephritis (1.9±0.3/3±0.4 mg/dL, p=0.633 and 2.5±0.4/3±0.3 mg/dL, p=0.573, respectively) (Fig. 4a, b).

Serum phosphate levels were found to be significantly correlated with platelet count in children with jSLE nephritis (r=0.755, p=0.031, respectively) (Fig. 5), while serum UA levels are strongly inversely correlated with D-dimer (r=–850, p=0.007) in these patients. Neither phosphate nor UA levels were correlated with serum creatinine levels or urine protein/creatinine ratios (p>0.05).

Discussion

Recent studies of jSLE have identified several promising biomarkers to aid in the monitoring of patients, while a single reliable, easily measureable biochemical marker is lacking for the determination of jSLE patients with AP and/or nephritis. Hence, pediatric studies of non-invasive biomarkers are of utmost importance. In this paper, we found the classical follow-up parameters to be higher in children at the AP of jSLE than those at RP (Table 1). It is worthy of note that serum phosphate and UA levels were more significantly decreased in the AP than in the RP. To the best of our knowledge, there has been only one study of jSLE and hypophosphatemia, while the relationship between UA and jSLE has yet to be ascertained in literature. The alterations to the phosphate and UA metabolism during the AP of jSLE are still unclear. Classically, hypophosphatemia may be

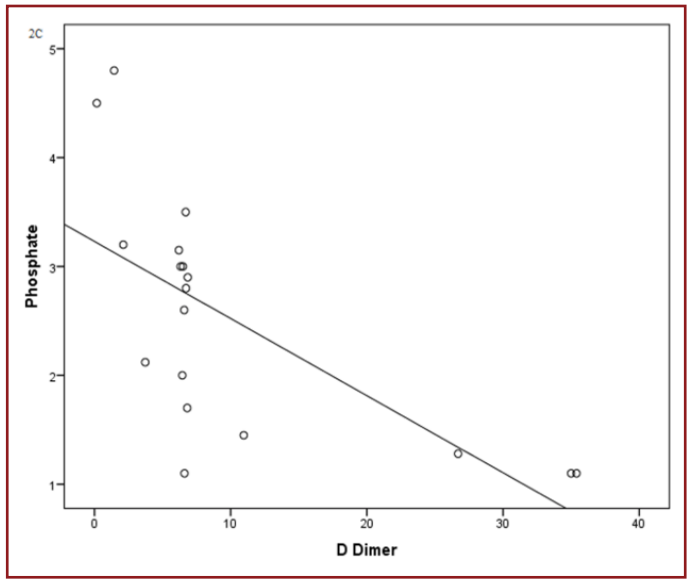

Figure 2. The phosphate and D-dimer correlations in patients with marked hypophosphatemia.

Table 4. Laboratory results of the patients according to the phosphate and uric acid levels

	Serum phosphate (<2.5 mg/dL) (n=8)	Serum phosphate (>2.5 mg/dL) (n=10)	Serum Uric acid (<2 mg/dL) (n=6)	Serum uric acid (>2 mg/dL) (n=12)	p
Anti-double-stranded DNA (U/mL)	4.1±1.3	4.3±1.9	4.2±1.8	4.2±1.5	P1. P2=NS
C-reactive protein (mg/dL)	9.1±2.7	5.4±3.5	9±3.7	6±3	NS
Complement C3 (mg/dL)	42±7.5	86±11.4	44.1±10	77.6±11	P1=0.008 P2=NS
Fibrinogen (mg/dL)	504.6±78	426.5±31.3	429±82	477.3±43.1	NS
Hemoglobin (g/dL)	9.2±1.5	10.9±0.7	9.7±2	10.3±0.7	P1. P2=NS
Platelet count (mm3)	88,750±20,982.9	198,900±22,486.8	77,000±26,460	186,416.7±20,448.9	P1=0.003 P2=0.013
Erythrocyte sedimentation rate (mm/h)	97.6±11.3	50.4±10.7	87.5±11.2	63.3±12.7	P1=0.008 P2=NS
Creatinine (mg/dL)	2.21±0.7	0.6±0.06	2.5±0.9	0.8±0.1	P1=0.04 P2=NS
Albumin (gr/dL)	2.4±0.2	3.9±0.2	2.3±0.3	3.7±0.3	P1=0.018 P2=0.002
D-dimer (mg/L)	16.5± 4.8	5±0.8	20.2±5.6	5±0.7	P1=0.034 P2=0.001
Phosphate (mg/dL)	-	-	1.3±0.1	3.1±0.2	P2=0.0001 P2=NS
Uric acid (mg/dL)	2±0.4	3.4±0.1	-	-	NS
Urine protein/creatinine ratio	1.4±0.5	0.6±0.2	1.4±0.6	0.8±0.3	P1.P2=NS

P1=Serum phosphate (<2.5 mg/dL) versus serum phosphate (>2.5 mg/dL), P2=Serum uric acid (<2 mg/dL) versus serum uric acid (>2 mg/dL), P3=With nephritis versus without nephritis.

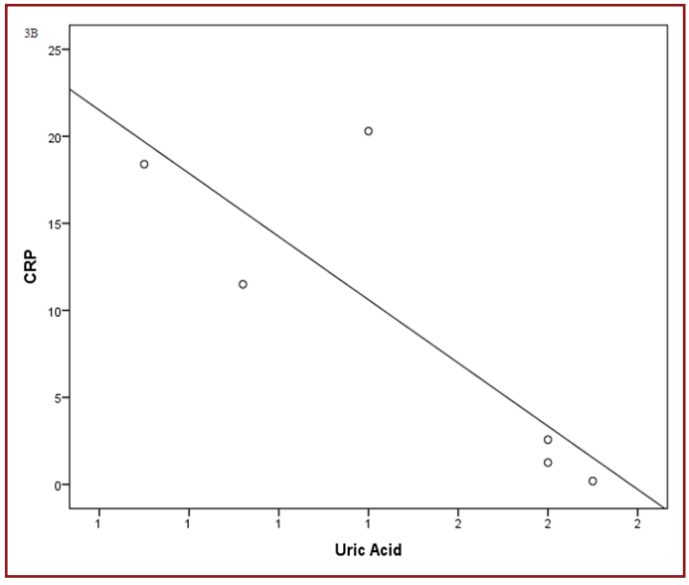

Figure 3. The uric acid and CRP correlations in patients with marked hypophosphatemia.

caused by the decreased intestinal absorption, increased renal excretion, or internal redistribution of inorganic phosphate[16]. Similarly, hypouricemia may be associated with defects in the production of UA or defects during the proximal tubular transport of UA[17]. Our findings suggest that reduced serum phosphate and UA levels will lead to an unusual metabolism in jSLE. A significant correlation was identified between phosphate levels and albumin, D-dimer and platelet count in our jSLE patients with AP, and similar relationships were also noted for UA. Moreover, the inverse correlation between phosphate and D-dimer persisted in patients with marked hypophosphatemia in AP, indicating that albumin, D-dimer, and platelet count could be indicators of inflammation and/or disease activity. This led us to believe that hypophosphatemia and hypouricemia may be related with acute inflammation and disease activity in jSLE patients. Inflammatory cytokines may lead to an internal redistribution of phosphate and UA. In a previous study, lipopolysaccharide and TNF-alpha induced the iPTH and downregulated the renal type IIa sodium-dependent phosphate cotransporter gene expression in mice, and the researchers reported an increase in phosphate excretion[18]. Barak et al.[19] also reported serum phosphate levels to be negatively correlated to inflammatory cytokines including interleukin-6 and TNF-alpha.

Table 5. Laboratory results in patients with nephritis

	Nephritis (Mean±SEM)		
	+ (n=8)	– (n=10)	p
Anti-dsDNA(U/mL)	7.2±2.1	1.8±0.5	0.04
C-reactive protein (mg/dL)	6.8±2.2	7.3±3.8	NS
Complement C3 (mg/dL)	49.3±10.9	80.2±11.8	NS
Fibrinogen (mg/dL)	469.1±68.9	454.9±45.9	NS
Hemoglobin (g/dL)	8.3±1.3	11.5±0.6	0.04
Platelet count (mm^3)	122,375±26,740.7	172,000±28,499.5	NS
ESR (mm/h)	89±11.1	57.3±13.2	NS
Creatinine (mg/dL)	2.3±0.6	0.6±0.04	0.0001
Albumin (gr/dL)	2.6±0.3	3.7±0.2	0.01
D-dimer (mg/L)	12.8±4	7.9±3.1	NS
Urine protein/creatinine	1.76±0.4	0.4±0.2	0.009

Anti-dsDNA: Anti-double-stranded DNA; ESR: Erythrocyte sedimentation rate.

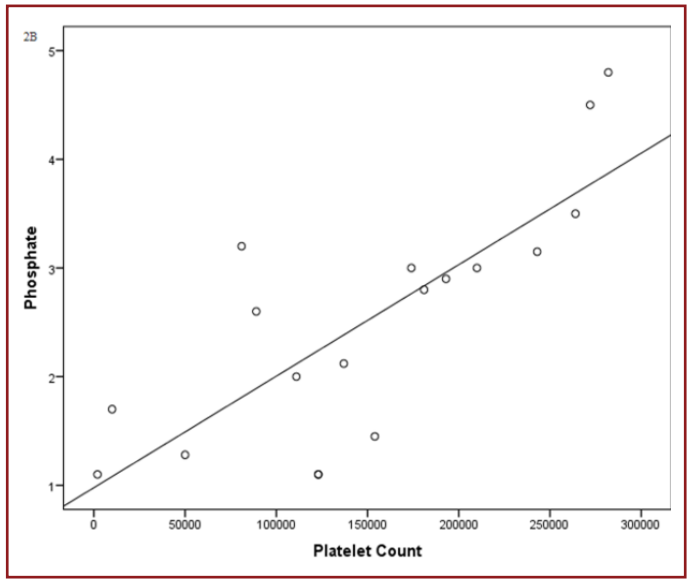

Figure 5. Serum phosphate and platelet correlations in patients with nephritis.

Oxidative stress plays an important role in the pathogenesis of SLE,[20,21] while UA is an important component of the plasma antioxidant capacity in the body. To the best of our knowledge, the relationship between UA and SLE has not been studied to date. In addition, it has been reported that serum UA levels were decreased in such inflammatory statuses as severe sepsis and are correlated with albumin, tocopherol-carrying lipoproteins, and transferrin which account for most of the antioxidant capacity of plasma[22]. In the present study, hypouricemia may be a reflection of the deterioration in plasma antioxidant capacity in AP.

Anti-dsDNA antibody levels often correlate with lupus activity and could be elevated in the inactive period in some patients[23]. We found anti-dsDNA antibodies to be elevated in 11 patients with AP, while anti-dsDNA levels were not correlated with any biochemical parameters including phosphate and UA levels, which may be due to heterogeneity in the pathogenic nature of anti-dsDNA. This marker is associated with their poly-reactivity and their ability to bind directly to non-DNA cross-reactive tissue antigens[23,24]. In contrast to the anti-dsDNA-related correlations, phosphate and UA levels were correlated with acute-phase markers in jSLE patients with AP. Our findings suggest that the serum phosphate and UA levels may be a better indicator than an-

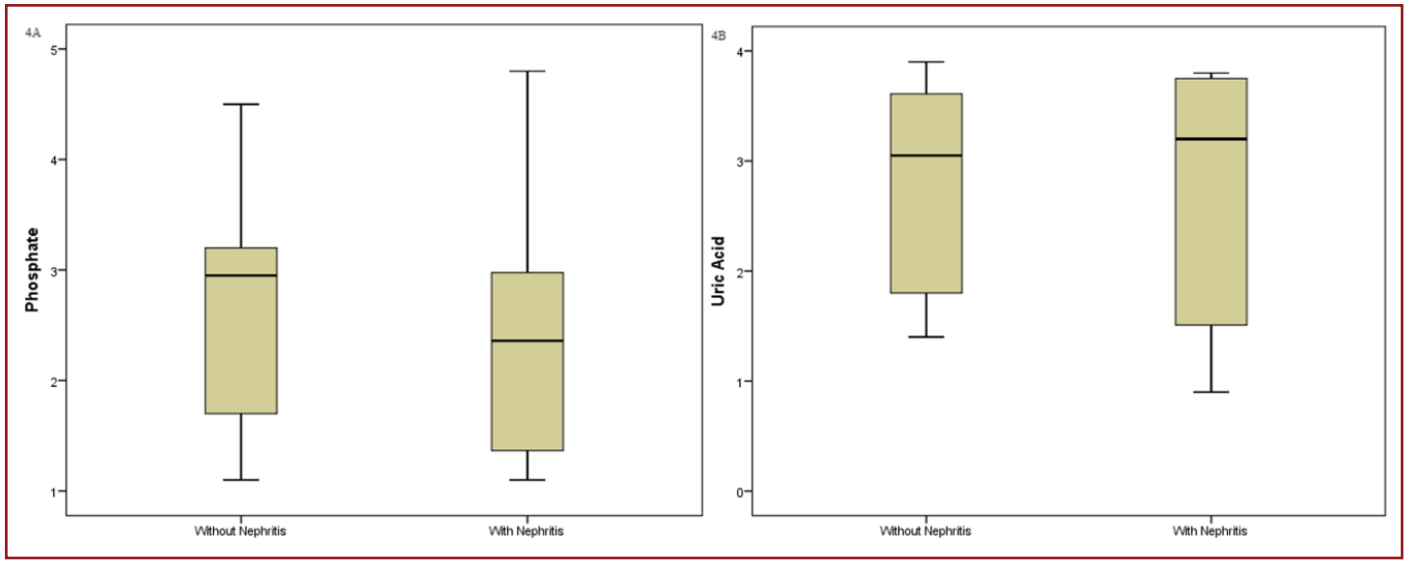

Figure 4. (a, b) Serum phosphate and uric acid levels in patients with and without lupus nephritis.

ti-dsDNA for the determination of AP in jSLE patients. Further studies are needed to determine the value of serum phosphate and UA levels as a sign and/or disease activity marker of jSLE.

Renal disease, referred to as lupus nephritis, occurs in 50–75% of all jSLE patients,[25] and can result in damage to the tubulointerstitial area, as well as to the glomerular and vascular compartments of the kidney[26]. In the present study, eight of the 18 patients had biopsy-proven nephritis, and so a possible mechanism behind hypophosphatemia and hypouricemia in jSLE may be their loss from renal tubules in AP. In Fujiwara et al.'s [27] study of four moderately and two markedly low hypophosphatemia jSLE patients, it was concluded that both TNF-α and IL-6 levels could be related to hypophosphatemia in jSLE patients, and that waste phosphate from renal tubules could feature in the mechanism of hypophosphatemia in SLE. We did not calculate the tubular phosphate reabsorption ratio or fractional UA excretion of the patients in the present study, but the lack of any correlation between phosphate and/or UA levels and serum creatinine and urine protein/creatinine ratios in patients with and without nephritis suggests that hypophosphatemia and hypouricemia are not associated with the increased excretion of these molecules in jSLE nephritis.

There are some limitations in our study that include the higher frequency of females in our groups, the relatively small number of the patients. Moreover, long-term follow-up results of the patients could not be obtained.

Serum phosphate and UA levels may be considered two useful indicators of SLE activation. Prospective studies are needed to clarify whether serum phosphate and UA levels could be predictors of AP in jSLE patients.

Ethics Committee Approval: This study was approved by the Ethics and Research Committee of the Duzce University (2021/No:18).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: N.M.S.; Design: N.M.S., B.Y.; Data Collection or Processing: N.M.S., N.Ç.; Analysis or Interpretation: N.M.S., N.Ç., B.Y.; Literature Search: N.M.S.; Writing: N.M.S., B.Y.

Conflict of Interest: None declared.

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