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Hypophosphatemia and Hyponatremia in Systemic Lupus Erythematosus Patients and Its Relation to Clinical Characteristic and Disease Activity

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ABSTRACT

Background: Systemic Lupus Erythematosus (SLE) is a chronic auto-immune disease with diverse manifestations, ranging from mild rash or arthritis to severe organ-threatening involvement.

Objective: The aim of the work was to find-out the possible association of hypophosphatemia and hyponatremia with disease activity in SLE patients.

Patients and methods: A total of 100 patients with SLE were involved in this study and the serum level of sodium and phosphorus, erythrocyte sedimentation rate (ESR), leucocytic and platelet counts, and 24 hr. protein were measured. SLE disease activity index (SLEDAI) score was assessed,

Results: The majority of patients were females; 94 (94%) and 6 males (6%) (F:M 15.7:1). The age of the patient ranged from 17 to 63 years with a mean age of 34.23 ±11.19 years. The disease duration was 48±55.7 months. 7. 41% of SLE patients were hyponatremic and 49% showed normonatremic. There was a significant correlation between Na level, SLEDAI score, vasculitis and arthritis and insignificant correlation with ESR. 47 patients were hypophosphatemic (47%) and 53 (53%) were normophophatemic. There was a significant correlation between phosphate level and SLEDAI, oral ulcers p=0.001 and arthritis p<0.0004 but negatively related with ESR.

Conclusion: It could be concluded that hyponatremia and hypophosphatemia are significantly related to SLEDAI, so it could be used as indicators of SLE activity and sever inflammation.

Keywords: Systemic lupus erythematosus, Hypophosphatemia, Hyponatremia, SLEDAI score.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic auto-immune disease with diverse manifestations, ranging from mild rash or arthritis to severe organ-threatening involvement [(1)].

SLE in Egypt shares many similarities with that in other nations. At the same time, several different clinical and immunologic characteristics are displayed even within the same country. Autoantibodies are present in a comparable number of patients as shown worldwide. Genetic and/or climatic factors may lead to different presentations of lupus and subsequent different therapeutic regimens [(2)].

Systemic lupus Erythematosus (SLE) is a typical autoimmune disease which adversely affects multiple end-organs, including heart, joints, liver, and kidneys. Hyper activation of autoantibodies against cell nucleic antigens leads to the deposition of immune complex in end organs [(3, 4)].

Common manifestations may include arthralgia and arthritis, malar and other skin rashes, pleuritis or pericarditis, renal or CNS involvement, hematologic cytopenia and weight changes are the most common symptoms in new cases or recurrent active SLE flares [(5)], with abnormal laboratory data, such as pancytopenia, low serum complement concentrations and positive autoantibodies against nucleus and DNA. Abnormalities of phosphorus (P) have never been described [(6, 7)].

Lupus activity can be measured by many laboratory markers as aberrant production and imbalance of T-helper (Th1/Th2) cell cytokines which have been implicated in the pathogenesis of autoimmunity. Also Increased RDW is connected with active disease status of SLE patients. RDW could be used as a surrogate marker of the inflammation and correlated with the SLEDAI score [(8)].

Hypophosphatemia is observed not only in genetic diseases such as X-linked hypophosphatemia [(9)], autosomal dominant hypophosphatemia, and McCune–Albright syndrome [(10)], but also in acquired states including tumor-induced osteomalacia and malnutrition. Studies have revealed that fibroblast growth factor 23 seems to play a key role in phosphate metabolism [(11)]. Although mechanisms of hypophosphatemia in these conditions are not fully understood. A recent report showed that serum phosphate concentrations were decreased in early sepsis, and tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) were suggested to be causes of hypophosphatemia in this pathologic condition [(12)]. In SLE, those cytokines have been shown to be involved in the disease activity, which led us to speculate about whether Phosphate metabolism in SLE might be aberrant, especially in patients with active disease [(9)].

Hyponatremia is defined as a serum sodium level that is less than 135 mEq/L. It is a common water balance disorder, with multiple causes including,

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syndrome of inappropriate secretion of antidiuretic hormone (SIADH), diuretics use, adrenal insufficiency, liver cirrhosis and heart failure [13]. Hyponatremia is presented mainly by central nervous system (CNS) dysfunction and is more dramatic with acute and marked decrease of serum sodium (Na) levels. Hyponatremic encephalopathy occurs as the result of the brain swelling secondary to acute hyponatremia and is associated with 34% risk of mortality [14]. Hyponatremia could reflect disease activity in children and adults with SLE [15]. Hyponatremia in SLE patients is related mainly to renal disease and the use of drugs as cyclophosphamide (CYC) [16]. However, hyponatremia in SLE has been reported and showed the association of SIADH with neuropsychiatric lupus [17, 18].

The aim of the present study was to find-out the possible association of hypophosphatemia and hyponatremia with disease activity in SLE patients.

PATIENTS AND METHODS

This study included a total of 100 adult SLE, attending at Department of Rheumatology, Sohag University Hospital.

Inclusion Criteria: Patients who fulfilled the criteria of Systemic Lupus International Collaborating Clinics (SLICC) classification [19].

Exclusion Criteria: SLE patients with secondary antiphospholipid syndrome (APS) or with other autoimmune diseases. Also, Patients with renal, hepatic or heart failure and those taking CYC or diuretics were excluded.

Ethical consent:

An approval of the study was obtained from Sohag University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients were divided according to serum Na levels into: Group I (hyponatremia n=41) with a level less than 135 mEq/L and those without hyponatremia (n = 59) group II. Also, the same patients were divided according to serum phosphorus levels into Group I (hypophosphatemia n=47) with level of phosphorus less than 2.5 and those without (hypophosphatemia n=53). SLE disease activity index (SLEDAI) [20] was assessed. Patients with a score less than 4 were considered in remission, while those with a score > 4 were considered active [20]. The number of active SLE patients were 83 while those in remission were 17 patients. Blood samples were drawn from all patients after they had fasted overnight. All laboratory analyses were performed on the same day within one hour of samples collection. Serum sodium, phosphorus, complements (C3 and C4) determination, complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver and kidney function tests were done. Serum, anti-nuclear antibodies (ANA) were quantitatively measured by immunofluorescence. Medications received by the patients were recorded. SLE disease activity index (SLEDAI) [20] was assessed. A serum sodium level <135 mEq/L was considered hyponatremia while a serum phosphorous level < 2.5 mEq/L was considered hypophosphatemia.

Statistical analysis

Data was computed and analyzed via IBMSPSS-20 computer program. Data was presented as means ± standard deviation (SD), median and inter quartile range or numbers and percentages. The results were examined for normality via Shapiro-Wilk test. The Mann–Whitney test and Spearman's correlation were employed. Chi-square (v2) test and Fisher's exact test were considered. ROC/Regression. P-value < 0.05 was considered significant.

RESULT

100 SLE patients were assessed by SLEDAI activity score and correlated with sodium were included in this study with 94 females (94%) and 6 males (6%) with a mean age of 34.2 ±11.19years. Patients with hyponatremia (n = 41) were 5 males and 36females with a mean age of 33.2±9.67 years while patients without (n = 59) were 3 males and 56 females with a mean age of 34.84±12.3years. The clinical manifestations in patients with and without hyponatremia show insignificant correlation with ESR (p=0.7), low platelet (p=0.5), low WBCs (p=0.09) and significant correlation with SELDIA score(p=<0.0001), vasculitis (p=0.003), proteinuria (p=0.006) and arthritis (p=0.006) (Table 1).

Table (1): Correlation between hyponatremia and different parameter of SLE activity, lab parameters and medication.

	Parameter	SLE patients (n = 100)		p
		Hyponatremia (n = 41)	without hyponatremia (n = 59)	
Age (years)		33.2±9.67	34.84±12,3	0.645
Gender F:M		36:5	56:3	0.032
Disease duration (months)		41.3 ±9.6	48.2±11.7	0.87
Clinical	Vasculitis	10	2	0.003
	Arthritis	18	11	0.006
	malar Rash	13	16	0.6
	New ulcer	15	6	0.002
	Alopecia	8	9	0.5
	Oral ulcer	30	31	0.03
	Fever	17	15	0.09
	New rash	4	7	0.6
	Frothy urine	23	13	0.001
Lab	Proteinuria	22	12	0.006
	Pyuria	5	7	0.002
	ALT (IU/L)	20.8 ± 4.08	18.76±3.18	0.322
	AST (IU/L)	24.3 ± 6.5	22.4±4.05	0.29
	Leucopenia	11	4	0.09
	Thrombocytopenia	10	4	0.5
	ESR (mm/hr.)	65.23±13.94	67.12±15.91	0.7
Medication	Azathioprien	23	27	0.4
	Mycnolate mofetil	4	5	0.8
	Hydroquine	15	35	0.04
	leflonamide	3	7	0.5
SLEDAI		7.72 ±1.41	3.9±0.913	<0.0001

The Patients also were assessed by SLEDAI activity score and correlated with phosphorus level the patient with hypophosphatemia (n = 47) were 4 males and 43females with a mean age of 32.8±9.75 years while patients without (n = 53) were 2 males and 51 females with a mean age of 35.66±12, 40 years. The clinical manifestations in patients with and without hypophosphatemia show insignificant correlation with ESR (p=0.5), low platelet (p=0.9), low WBCs (p=0.1) and significant correlation with SELDIA score (p=<0.0005), proteinuria (p=0.002) and arthritis (p<0.0004) (Table 2).

Table (2): Correlation between hypophosphatemia and SLE activity parameter, lab findings and medications.

	Parameter	SLE patients (n = 100)		P value
		Hypophosphatemia (n = 47)	Without Hypophosphatemia (n = 53)	
Age (years)		32.8±9.75	35.66±12,40	0.458
Gender F:M		43:4	51:2	0.4
Disease duration (months)		41.3 ±6.6	48.2±55.7	0.87
Clinical	Vasculitis	10	2	0.01
	Arthritis	23	6	<0.0004
	Malar Rash	13	16	0.8
	New ulcer	15	6	0.01
	Alopecia	11	6	0.1
	Oral ulcer	37	24	0.001
	Fever	17	15	0.5
	Frothy urine	26	24	<0.0001
Lab	Proteinuria	25	9	0.002
	Pyuria	13	12	0.006
	ALT (IU/L)	21.6 ± 4.19	19.19±3.36	0.322
	AST (IU/L)	25.03 ± 4.97	23.46±4.89	0.29
	Leucopenia	11	4	0.1
	Thrombocytopenia	3	4	0.9
	ESR (mm/hr.)	67.62±13.91	55.53±14.61	0.5
Medication	Azathioprien	26	24	0.4
	Hydroquine	19	31	0.1
	Leflonamide	2	8	0.09
	Mycnolate mofetil	6	3	0.2
SLEDAI		7.72 ±1.41	3.9±0.913	<0.0005

The patients were divided into no activity, mild, moderate and high disease and very high activity by SLEDIA,17patient had no activity (SLEDAI=0) 28 patient had mild(SLEDAI =1-5), 25 had moderate disease activity (SLEDAI = 6-10), 24 patient had severe disease activity (SLEDAI = 11-19) and 6 patient had very high disease activity (SLEDAI= >20) in table3 and compare them in hyponatremia and hypophosphatemia in figure 1 and figure2 show that more hyponatremia and hypophosphatemia associated with more sever disease activity.

Table (3): Grading of severity of activity.

GRADING of severity of activity

		Frequency	Percent
Valid	No	17	17.0
	mild	28	28.0
	moderate	25	25.0
	severe	24	24.0
	very high	6	6.0
	Total	100	100.0

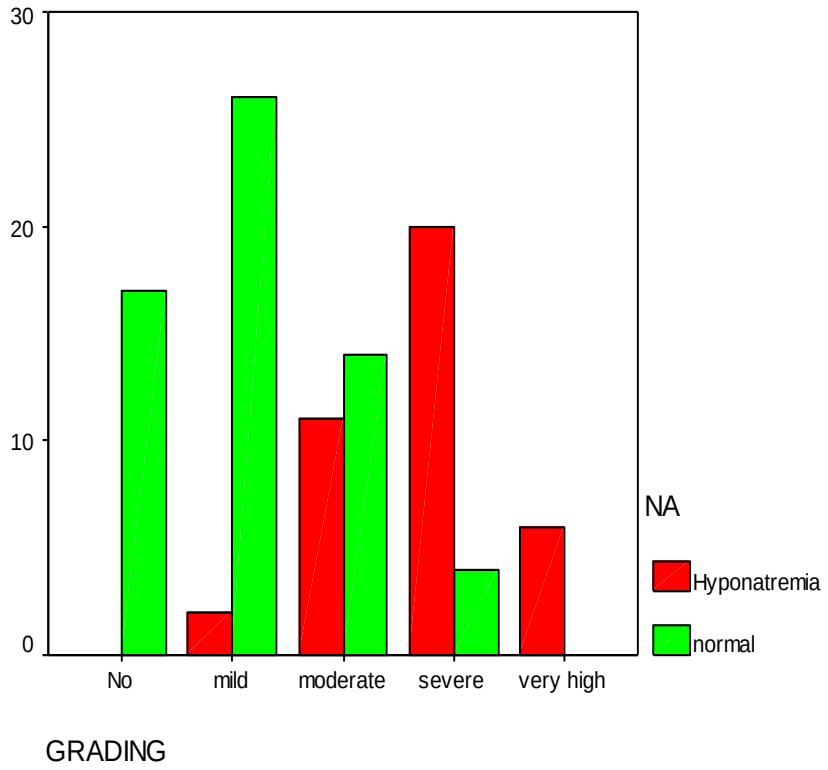

Figure (1): The relation between hyponatremia and grading of severity of activity.

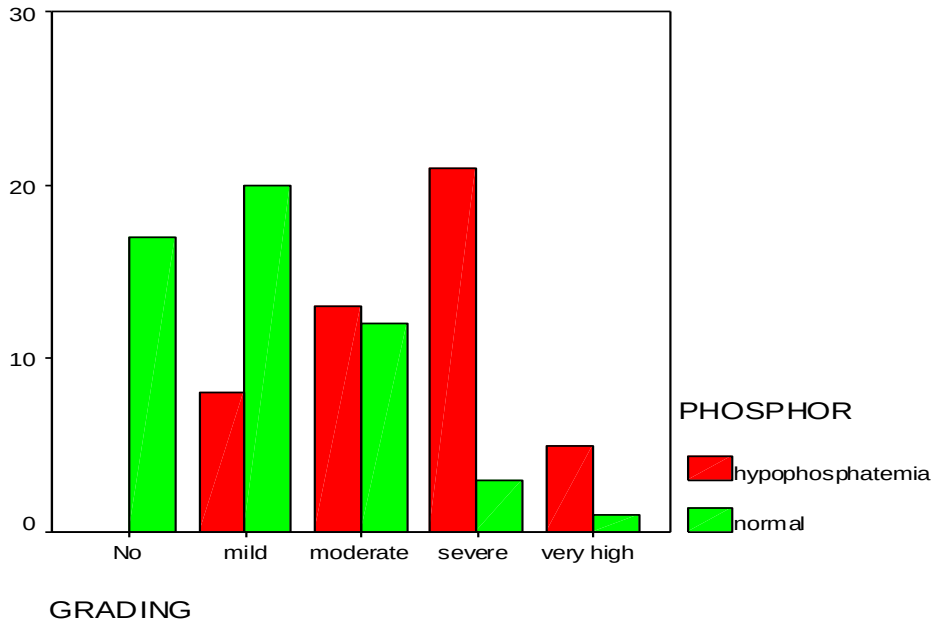

Figure (2): The relation between hypophosphatemia and grading of severity of activity.

DISCUSSION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between people and may be mild to severe. Often there are periods of illness, called flares, and periods of remission during which there are few symptoms [21, 22]. In our study 100 SLE patients were assessed by SLIDE activity score and correlated with sodium and phosphorus levels to investigate relation and effect of hyponatremia and hypophosphatemia as indicators for activity.

patients included in this study were 94 females (94%) and 6 males (6%) with a mean age of 34.23 ±11.19 years. The age is symmetrical in distribution of age group to SLE affection and activity with agreement with other authors, **El-Badawy *et al.*** [16] **and Yamany** [23] and asymmetrical in distribution to **Shin *et al.*** [15], who done his study on child and adult with SLE, and **Fujiwara *et al.*** [10] who done his study on juvenile SLE patient.

In our study sex distribution wear 94 females (94%) and 6 males (6%), which is same as gender affection in other series **Shin *et al.*** [15]**, El-Badawy *et al.*** [16] **and Yamany** [23], with different gender distribution with other series e.g., **Fujiwara *et al.*** [10] who did his study on female gender only and juvenile which may explain some differences in result.

The mean duration of the disease in our series was 48 months, with SD± 55.75, and it ranged from 1 to 266 months. Same duration or near data from other series in comparison to our study [15, 16, 23].

In the current study, patient activity was divided according to SLEDAI to active and inactive. Activity again subdivided into mild, moderate, high and very high. Using of this universal score put our patient series in head-to-head comparison with other authors [15, 16, 23].

The current work hypothesized that low serum sodium level and low phosphorus level could be a determinant of lupus inflammatory activity. Hence, the aim of the study design was to evaluate both hypophosphatemia and hyponatremia in lupus disease. The other variable factors including medications, namely diuretics, and renal sodium loss due to renal tubular injury and tubular membrane damage, leading to acute kidney injury (AKI) [24]. So, those patients with tubule-interstitial nephritis proven by renal biopsy were excluded from this study [23].

In our study SLE patients were assessed by SLEDAI activity score, ESR WBCS, Platelets were correlated with sodium and phosphorus levels to investigate the relation and effect of hyponatremia and hypophosphatemia as indicators for activity.

We found that serum Na levels significantly correlated to vasculitis, arthritis and oral ulcers, all in favor that hyponatremia in SLE patients is directly related to more severe activity and inflammation. In accordance, the association of hyponatremia with SLEDAI, decreased C3 and increased ESR levels in juvenile SLE cases has been demonstrated in addition to a negative relation of serum sodium with serum IL-6 levels was found in adult SLE patients [15]**.**

Fujiwara *et al.* [10] reported that the reason for significant correlation of serum P with anti-single-stranded DNA antibody, not with dsDNAab, is uncertain; however, it might be due to heterogeneity in pathogenesis of SLE.

In our study we found that hypophosphatemia is correlated positively to SLEDAI and arthritis and correlated negatively to ESR, platelet and WBCs.

Further studies are necessary to study the pathophysiology of hypophosphatemia and hyponatremia in SLE.

CONCLUSION

It could be concluded that hyponatremia and hypophosphatemia are significantly related to SLEDAI, so it could be used as indicators of SLE activity and sever inflammation.

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