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ORIGINAL ARTICLE

Association between levels of serum and urinary B cell-activating factor and systemic lupus erythematosus disease activity

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ABSTRACT

Objectives: This study investigated the correlation between serum and urinary B cell-activating factor (BAFF) levels and systemic lupus erythematosus (SLE) disease activity.

Patients and methods: This case-control study was conducted with 87 participants between December 2020 and September 2021. Sixty-two SLE patients who fulfilled the eligibility criteria were enrolled. SLE patients were categorized into active (n=34) and inactive (n=28) groups based on their Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores. The control group consisted of 25 healthy subjects. Serum and urine samples were collected for the measurement of BAFF levels. Finally, the relationship between these variables and SLE disease activity was investigated.

Results: The mean age of active (SLEDAI-2K >4) and inactive (SLEDAI-2K ≤4) SLE patients and healthy individuals were 32.8±7.8, 32.5±6.8, and 31.7±7.8 years, respectively (p=0.62). The median serum BAFF (s-BAFF) and urinary BAFF (u-BAFF) in active lupus patients (10.4 [2.3] ng/mL and 8.2 [3.7] ng/mL, respectively) were significantly higher than in inactive lupus patients (6 (7.1) ng/mL and 1.7 (4.7) ng/mL, respectively; p<0.001) and the control group (3 (3.7) ng/mL and 1.6 (2.2) ng/mL, respectively; p<0.001). However, s-BAFF (p=0.07) and u-BAFF (p=0.43) did not significantly differ between the inactive group and the control group. A significant positive correlation was observed between s-BAFF (r=0.41 and p=0.001) and u-BAFF (r=0.78 and p<0.001) levels and the SLEDAI-2K score.

Conclusion: There is a significant positive correlation between serum and urinary BAFF levels and SLE disease activity. Furthermore, significantly higher levels of s-BAFF and u-BAFF have been observed in patients with active lupus compared to inactive and healthy subjects, indicating a possible role for BAFF in the pathogenesis of SLE disease activity.

Keywords: B cell-activating factor, SLEDAI-2K, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is an autoimmune disease whose etiology remains elusive, with various manifestations that can lead to organ damage.[1,2] The estimated incidence of SLE is 1 to 25 per 100,000 in Asia, Europe, and the USA.[3] Complement levels and double-stranded deoxyribonucleic acid (dsDNA) antibodies (anti-dsDNA) have been the primary serological markers for disease activity in SLE patients.[4,5] However, the need for a more accurate clinical biomarker evaluating the risk of SLE flare-ups has always been felt.

B cell-activating factor (BAFF) is a member of the tumor necrosis factor family, which

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seems to have a role in the pathogenesis of SLE disease. It is mainly secreted from the myeloid cells and plays an essential role in B cell survival and differentiation. BAFF is involved in SLE pathogenesis by helping to protect self-activated B cells from being eliminated (negative selection process).[6,7] In addition to SLE, BAFF is presumed effective in the pathogenesis of other autoimmune disorders, such as primary Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis.[8-10]

Animal studies have revealed that mice with higher BAFF levels showed a phenotype similar to SLE and had elevated dsDNA levels. Several studies have also indicated that BAFF levels are increased in SLE patients, specifically those with nephritis and central nervous system involvement.[11,12] Although several studies have been performed on this topic, the results are contradictory regarding the relationship between serum BAFF (s-BAFF) levels and SLE activity. Furthermore, few studies have measured urinary BAFF (u-BAFF) levels in SLE patients and have not evaluated its correlation to SLE disease activity. Finally, no study has been conducted on this issue in the Iranian population. The current study aimed to investigate the relationship between the serum and urinary levels of BAFF with SLE activity.

PATIENTS AND METHODS

Study design and participants

This case-control study was performed with 87 participants at the (12 males; 75 females; mean age: 32.3±7.4 years; range, 18 to 52 years) at the Rheumatology wards of Ghaem and Imam Reza Hospital between December 2020 and September 2021. The eligibility criteria for SLE patients were *(i)* patients diagnosed according to the 2010 American College of Rheumatology (ACR) classification criteria[13] by an expert rheumatologist and *(ii)* those diagnosed with SLE for at least 36 months. The exclusion criteria were as follows: *(i)* pregnancy, *(ii)* diagnosis of other autoimmune and autoinflammatory disorders, *(iii)* underlying diseases, including liver cirrhosis, chronic lymphocytic leukemia, Hodgkin, and non-Hodgkin lymphoma, *(iv)* smoking, *(v)* history of chemotherapy (cytotoxic drugs), rituximab, and belimumab use, *(vi)* systemic or local infection (e.g., human immunodeficiency virus and hepatitis C), and *(vii)* a glomerular filtration rate <50 mL/min/1.73 m^2.

Systemic lupus erythematosus disease activity was stratified into active and inactive groups based on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores;[14] patients with SLEDAI-2K scores >4 and SLEDAI-2K scores ≤4 were considered to be in the active (n=34) and inactive (n=28) SLE groups, respectively. The control group participants (n=25), matched for age and sex, were selected from the healthy companions of the SLE patients.

Variables and data collection

SLEDAI-2K score is calculated based on 24 descriptors in nine organ systems over the preceding 30 days by an expert rheumatologist. Fifty mL of morning mid-stream urine and 20 mL of blood from the antecubital vein after 8 h of fasting were collected from each participant. These samples were centrifuged immediately and kept at -80°C. ELISA kits, designed by Bioassay Technology Laboratory (Shanghai, China), were used to measure BAFF levels in the urine and blood samples.

Other variables include demographic data (age and sex), past medical history (nervous system, renal, cutaneous, musculoskeletal, serological, hematological, and visceral manifestations, fever, vasculitis, and serositis), drug history (prednisolone, hydroxychloroquine, and immunosuppressant use), laboratory data (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], antinuclear antibodies (ANA), dsDNA, ANA profile (including anti-Ro, anti-La, and anti-Sm [Smith]), decreased complement (C) 3 and C4 levels, antiphospholipid antibodies (anticardiolipin immunoglobulin [Ig] G, anti-β2-glycoprotein IgG, lupus anticoagulant, anticardiolipin IgM, and anti-β2-glycoprotein IgM), leukopenia, lymphopenia, thrombocytopenia, liver function tests, and proteinuria were gathered by completing a prepared checklist through interview and patients' hospital files.

Statistical analysis

IBM SPSS version 21.0 software (IBM Corp., Armonk,, NY, USA) was used in order to

calculate the sample size, and the outcome used to calculate the sample size was the mean BAFF in the two groups (active and inactive). Considering an alpha error of 0.05 and power of 80%, according to the mean BAFF levels in Zhao et al.'s[15] study, eight participants were required for each group; however, to increase the study power, the sample size was increased to 25 in each group.

The Shapiro-Wilk test was used to assess the normality of data, which showed the nonnormal distribution of s-BAFF and u-BAFF levels. The Kruskal-Wallis test compared these two variables between the study groups. Additionally, Pearson's correlation test was utilized to assess the correlation between s-BAFF and u-BAFF levels and SLEDAI-2K scores. To compare normally distributed quantitative data and qualitative data between study groups, one-way analysis of variance and the chi-square were used, respectively. Furthermore, the independent samples t-test and the Mann-Whitney U test were used for comparing the quantitative data between the active and inactive SLE groups with normal and nonnormal distributions, respectively. The significance level was considered $p<0.05$, except for the two-by-two comparison tests conducted after the Kruskal-Wallis test, for which the significance level was corrected using Bonferroni correction (0.05/3=0.017).

RESULTS

Participants and baseline characteristics

The mean age of active SLE patients, inactive SLE patients, and healthy individuals was 32.8±7.8, 32.5±6.8, and 31.7±7.8 years, respectively (p=0.62). Most participants were female in all three groups, with 82.4% in the active SLE, 85.7% in the inactive SLE, and 92% in the control group (p=0.57). The most prevalent manifestations in active lupus patients were renal (52.9%), cutaneous (38.2%), and musculoskeletal manifestations (38.2%). Furthermore, the most common findings of inactive lupus patients were hematological involvement (25%) and fever (17.9%). While ANA was the most common laboratory finding in both active and inactive SLE patients, ESR, CRP, lymphopenia, and proteinuria were only evident in the active patients (Table 1).

Serum BAFF

The median (interquartile range [IQR]) s-BAFF level in the active, inactive, and control group was 8.2 (3.7), 6 (7.1), and 3 (3.7) ng/mL, respectively ($p<0.001$). Moreover, a subsequent two-by-two comparison demonstrated that the median s-BAFF in active lupus patients was significantly higher than that of inactive SLE patients ($p<0.001$) and the control group ($p<0.001$). However, this figure did not significantly differ between the inactive and control groups (p=0.07, Figure 1).

A significant positive correlation was shown between SLEDAI-2K and s-BAFF (r=0.41, p=0.001, Figure 2). Furthermore, patients with serositis and vasculitis had higher s-BAFF levels than those without these diagnoses (p=0.03 and p=0.01, respectively). Among laboratory findings, s-BAFF was only significantly higher in patients with elevated CRP levels than in those with low CRP (p=0.004, Table 2). In the active lupus patients with cutaneous involvement, there was a significantly higher amount of s-BAFF than in those without it (p=0.02, Table 3).

Urinary BAFF

The median (IQR) u-BAFF level in the active, inactive, and control groups was 10.4 (2.3), 1.7 (4.7), and 1.6 (2.2) ng/mL, respectively ($p<0.001$). Subsequently, the between-group comparison showed that u-BAFF was significantly higher in the active SLE group compared to the inactive ($p<0.001$) and control groups ($p<0.001$). However, similar to the serum results, the u-BAFF levels had no significant difference between the inactive and control groups (p=0.43, Figure 1).

Regarding demographic data, clinical manifestations, treatment, and laboratory variables in SLE patients, the u-BAFF level was significantly higher in the presence of renal ($p<0.001$) and cutaneous (p=0.004) involvement. Additionally, significantly higher amounts of u-BAFF were observed when SLE patients developed musculoskeletal manifestation, serositis, and vasculitis ($p<0.001$, p=0.01, and p=0.01, respectively; Table 2).

Table 1. Demographics, clinical manifestations, treatment, and laboratory findings of subjects in the active lupus, inactive lupus, and control groups

	Active lupus group (n=34)					Inactive lupus group (n=28)					Control group (n=25)				
Characteristics	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR
Age (year)			32.8±7.8					32.5±6.8					31.7±7.8		
Sex															
Female	28	82.4				24	85.7				23	92			
Duration of illness (month)				37	27				36	27				-	-
SLEDAI-2K				14	6				2	2				-	-
Clinical manifestations															
Fever	11	32.4				5	17.9				-	-			
Nervous	11	32.4				0	0				-	-			
Renal	18	52.9				2	7.1				-	-			
Cutaneous	13	38.2				1	3.6				-	-			
Musculoskeletal	13	38.2				0	0				-	-			
Serositis	6	17.6				0	0				-	-			
Visceral	1	2.9				0	0				-	-			
Vasculitis	8	23.5				0	0				-	-			
Laboratory findings															
Elevated ESR	11	32.4				0	0				-	-			
Elevated CRP	27	79.4				0	0				-	-			
Leukopenia	5	14.7				1	3.6				-	-			
Lymphopenia	1	2.9				0	0				-	-			
Thrombocytopenia	7	20.6				3	14.3				-	-			
Abnormal LFT	1	2.9				1	3.6				-	-			
Urea			24	13				21	10		-	-			
Cr			0.8	0.7				0.8	0.4		-	-			
Proteinuria	15	44.1				0	0				-	-			
ANA	31	91.2				27	96.4				-	-			
dsDNA	16	47.1				6	21.4				-	-			
ANA profile	10	29.4				2	7.1				-	-			
Decreased C3	11	32.4				5	17.9				-	-			
Decreased C4	11	32.4				5	17.9				-	-			
Anti-phospholipid antibodies	6	17.6				6	21.4				-	-			
Hematologic involvement	12	35.3				7	25				-	-			
Treatment															
Prednisolone	24	70.6				7	25				-	-			
Hydroxychloroquine	32	94.1				21	75				-	-			
Immunosuppressant	13	38.2				3	10.7				-	-			

SD: Standard deviation; IQR: Interquartile range; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; LFT: Liver function test; Cr: Creatinine; ANA: Antinuclear antibodies; dsDNA: Double-stranded DNA. Anti-phospholipid antibodies, including IgG anticardiolipin, IgG anti-B2 glycoprotein, lupus anticoagulant, anticardiolipin IgM, and anti-B2 glycoprotein IgM.

Table 2. Comparison of serum and urinary BAFF levels (ng/mL) in SLE patients in terms of different variables

Characteristics		Serum BAFF			Urinary BAFF		
		Median	IQR	*p*	Median	IQR	*p*
Sex	Male	8.6	4.5	0.16	9.2	9.1	0.98
	Female	7.3	3		8.5	8.8	
	Fever						
	No	7.6	3.6	0.73	8.4	8.4	0.29
	Yes	6.9	4.5		10.1	7.7	
	Renal involvement						
	No	7.3	4.6	0.41	6.4	8.6	<0.001
	Yes	8	3.9		10	2.2	
	Cutaneous involvement						
	No	6.5	3.8	0.19	7.7	8.9	0.004
	Yes	9.3	2.7		9	2.4	
Clinical manifestations	Musculoskeletal involvement						
	No	7.3	4.4	0.14	7.1	8.8	0.005
	Yes	8.2	4.2		10.1	2.6	
	Serositis						
	No	7	3.7	0.03	8.4	8.8	0.04
	Yes	8.4	2.9		10.1	3.2	
	Vasculitis						
	No	7	3.1	0.01	8.3	8.6	0.01
	Yes	9.6	2.9		10.4	2.4	
	Prednisolone						
	No	6.9	5	0.10	5	8.8	0.002
	Yes	7.8	3.9		9.2	2.8	
Treatment	Hydroxychloroquine						
	No	7.5	6.4	0.39	1.7	9	0.07
	Yes	7.3	3.9		8.9	6.7	
	Immunosuppressant						
	No	7.2	2.6	0.10	7.1	8.5	0.001
	Yes	8.5	4.5		10.3	2.5	
Laboratory findings	Elevated ESR						
	No	7.3	4.4	0.37	7.2	9.1	0.01
	Yes	7.8	2.4		10.1	1.3	
	Elevated CRP						
	No	6.1	5.1	0.004	3.6	7.1	<0.001
	Yes	8.1	3.6		10.2	2.6	
	Leukopenia						
	No	7.4	3.8	0.77	8.5	8.6	0.22
	Yes	7.2	4.3		10	6.2	
	Thrombocytopenia						
	No	7.2	3.5	0.09	8.5	8.7	0.16
	Yes	8.1	4.2		10	4	
	Proteinuria						
	No	7.3	4.8	0.12	5.6	8.6	0.001
	Yes	8.2	3.7		10.2	2.2	
	ANA						
	No	8	2.6	0.28	10.5	7.7	0.25
	Yes	7.2	3.8		8.5	8.6	

Table 2. Continued

Characteristics		Serum BAFF Median	Serum BAFF IQR	Serum BAFF p	Urinary BAFF Median	Urinary BAFF IQR	Urinary BAFF p
	dsDNA						
	No	6.9	4.3	0.5	8.3	9.1	0.3
	Yes	7.7	2.9		8.8	5	
	ANA profile						
	No	7.2	3.9	0.59	8.4	8.6	0.06
	Yes	7.9	3.6		10.4	3.6	
	Decreased C3						
	No	7.1	4.4	0.15	8.4	8.9	0.04
	Yes	7.9	3.7		9.5	4	
	Decreased C4						
	No	7.1	4.4	0.15	8.4	8.9	0.04
	Yes	7.9	3.7		9.5	4	
	Anti-phospholipid antibodies						
	No	7.4	3.9	0.8	8.6	8.6	0.9
	Yes	7.3	2.5		7.2	10	
	Hematologic involvement						
	No	7.2	3.5	0.22	8.5	8.8	0.15
	Yes	8.1	3.6		9	4	

BAFF: B cell-activating factor; SLE: Systemic lupus erythematosus; IQR: Interquartile range; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: Antinuclear antibodies; dsDNA: Double-stranded deoxyribonucleic acid; Mann-Whitney U test has been used in order to compare the groups. Anti-phospholipid antibodies, including IgG anticardiolipin, IgG anti-B2 glycoprotein, lupus anticoagulant, anticardiolipin IgM, and anti-B2 glycoprotein IgM.

In terms of medications, u-BAFF differed significantly in patients who took prednisolone (p=0.002) and immunosuppressant (p=0.001) compared to those without these drug regimens. In terms of laboratory data, this figure was remarkably greater in the presence of elevated ESR and CRP, proteinuria, and low complement level. Consistent with s-BAFF findings, u-BAFF also had a significant positive correlation with the SLEDAI-2K score (r=0.78 and p<0.001). Regarding data of active lupus patients, u-BAFF was significantly different among patients with and without nervous system involvement (p=0.003, Table 3).

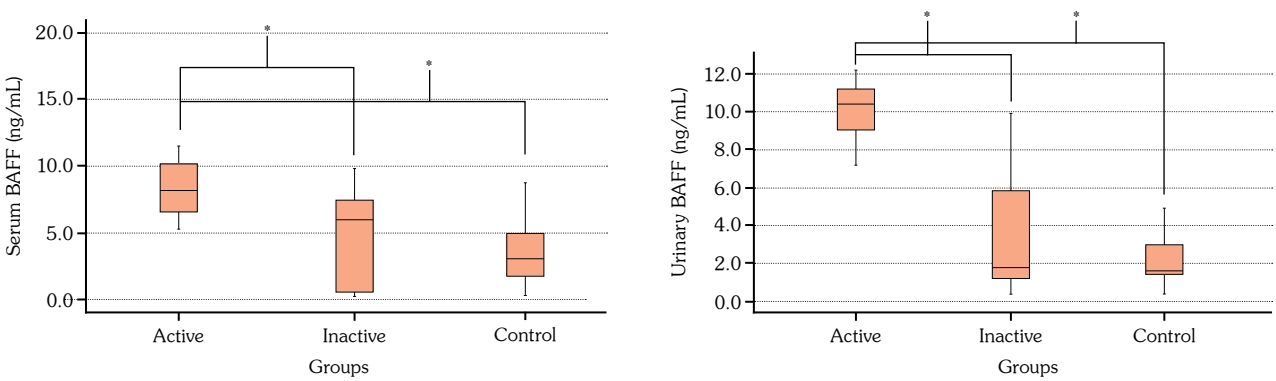

Figure 1. Comparison of the serum and urinary BAFF levels in patients with active lupus, inactive lupus and the control group.

BAFF: B cell-activating factor.

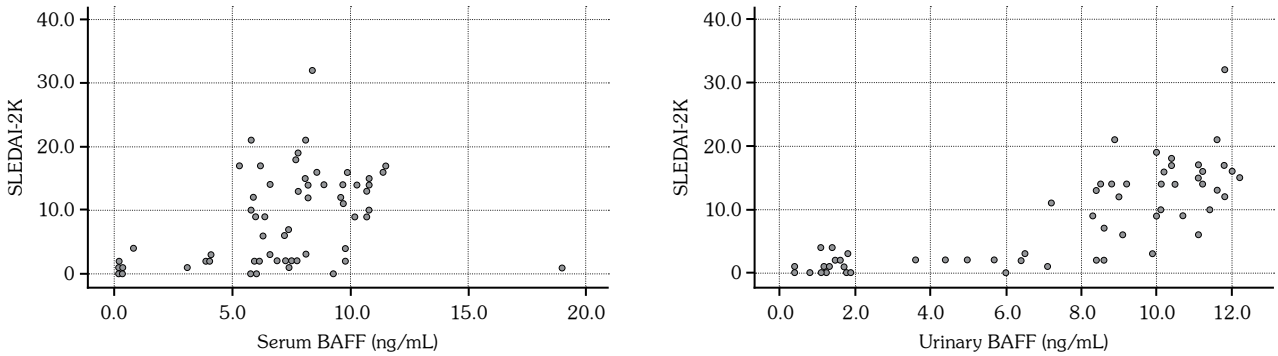

Figure 2. Correlation between the serum and urinary BAFF levels and SLEDAI-2K.
BAFF: B cell-activating factor; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 3. Comparison of serum and urinary BAFF levels (ng/mL) in patients with active lupus in terms of different variables of clinical manifestation and laboratory findings

	Serum BAFF				Urinary BAFF			
Characteristics	Mean±SD	Median	IQR	*p*	Mean±SD	Median	IQR	*p*
Fever								
No		8.2	2.5	0.66*	10.1±1.3			0.57
Yes		8.2	44.4		10.4±1.1			
Nervous involvement								
No		9.6	4.1	0.15*	9.8±1.2			0.003
Yes		8.1	2		11.1±0.7			
Renal involvement								
No		8.4	2.6	0.29*	10.2±1.5			0.96
Yes		8	4.1		10.2±1.1			
Cutaneous involvement								
No	8±1.9			0.02	10.6±1			0.15
Yes	9±1.6				9.6±1.4			
Musculoskeletal involvement								
No	8.5±1.8			0.73	10.2±1.3			0.67
Yes	8.2±2				10.1±1.3			
Serositis								
No		8.1	3.8	0.25*		10.4	2.2	0.87*
Yes		8.4	2.9			10.1	3.2	
Vasculitis								
No	8.1±1.8			0.64	10.1±2.3			0.15
Yes	9.2±1.9				10.4±1.1			
Serologic involvement								
No	8.1±2			0.69	10.3±1.1			0.56
Yes	8.5±1.8				10.1±1.3			
Hematologic involvement								
No	8.5±1.9			0.95	10.2±1.1			0.69
Yes	8.2±1.8				10.2±1.5			

BAFF: B cell-activating factor; SD: Standard deviation; IQR: Interquartile range; Independent sample T-test has been used unless stated otherwise.
* Mann-Whitney U test has been used. Serologic involvement was considered if a patient was positive for either ANA, dsDNA, or ANA profile.

DISCUSSION

Our results showed a significant positive correlation between s-BAFF and u-BAFF with the disease activity of SLE patients. Furthermore, these variables were significantly higher in active lupus patients compared to the control group, whereas no significant difference was found between the inactive and control groups. In the following, our results will be compared and discussed with the existing literature.

Evidence points towards a clear relation between BAFF overexpression, disease activity, and autoantibody production in SLE mouse models. BAFF overproduction in some transgenic mice leads to polyclonal hypergammaglobulinemia and an increase in multiple autoantibody titers, such as anti-dsDNA, circulating immune complexes, and renal immunoglobulin deposits.[16] In addition, mice genetically predisposed to SLE, such as NZBWF1/J and MRL/MpJ-Fas1pr/J mice, had higher circulating BAFF levels.[16] Moreover, treatment of these SLE mouse models with BAFF antagonists has been shown to slow the disease progression and improve survival.[17]

Along with animal studies, BAFF overexpression has been proven to be a feature of human SLE, which is present in 30% of patients.[18] Our results showed no significant difference in s-BAFF and u-BAFF between SLE patients with and without ANA, anti-dsDNA, and antiphospholipid antibodies. In line with our results, Elbirt et al.[19] found no significant correlation between the BAFF circulating level and anti-dsDNA due to the differences in measurement methods. In contrast, the correlation between BAFF circulating level and anti-dsDNA was first reported by Cheema et al.,[20] and some authors emphasized this finding afterward.[21,22] Furthermore, an association between serum BAFF level and anti-Sm antibody has also been revealed.[23] Therefore, BAFF overexpression has a significant role in autoantibody production.

There is controversy over the relationship between s-BAFF levels and lupus disease activity. Our study demonstrated a significant positive correlation between s-BAFF and u-BAFF levels and the SLEDAI-2K score. Most researchers agree that there is a significant correlation between the s-BAFF and SLE disease activity measured by the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI.[15,24-31] On the other hand, some studies did not conclude a relationship between this variable and SLE disease activity quantified by SELENA-SLEDAI and the Systemic Lupus Activity Measure.[11,19,21,26,32] Collins et al.[33] suggested that elevated BAFF mRNA (messenger ribonucleic acid) levels in peripheral blood mononuclear cells correlate more precisely with lupus disease activity than s-BAFF protein levels. There is also a debate over the longitudinal relation between changes in s-BAFF levels and SLE disease activity. Although some studies failed to demonstrate this relation,[32,34] Petri et al.[24] proved a correlation between BAFF circulatory levels and SLE disease activity in the longitudinal assessment of SLE patients. Preliminary analysis of phase 3 randomized clinical trials in this area (BLISS-52 and BLISS-76) indicated that an s-BAFF level >2 ng/mL is an independent prognostic factor for moderate to severe lupus.[35]

Regarding the role of BAFF in lupus nephritis, there were no significant differences in s-BAFF and u-BAFF levels between lupus patients with and without renal involvement in our study. However, BAFF expression has been reported in both mice and human renal tubular epithelial cells in relation to disease activity and histopathological activity index in SLE.[36] A 2017 study by Kang et al.[37] found that BAFF promotes lupus nephritis by stimulating renal tertiary lymphoid structures and regulating the position of T cells in glomeruli. Another study in 2020 by Aguirre-Valencia et al.[38] showed that u-BAFF, APRIL (a proliferation inducing ligand) signaling factor, and BLyS receptor 3 (BR3) mRNAs are suggested as helpful biomarkers in patients with lupus nephritis. Increased BAFF expression in glomeruli and elevated inflammatory factors were detected in Class 3 and 4 lupus nephritis, while low BAFF expression was observed in Class 5.[39] Although u-BAFF rose considerably in patients with lupus nephritis, it was not associated with disease activity.[40] Additionally, in a cohort study by Vincent et al.,[41] u-BAFF was detected in only a small proportion (12%) of SLE patients; however, this amount was notably higher in people with active kidney disease. According to Friebus-Kardash et al.'s[27] study,

the presence of the BAFF-var allele can lead to BAFF overproduction, which is associated with lupus nephritis. At the same time, no relationship was found between the BAFF-var allele and disease manifestations in another study.[42,43] Several clinical studies have reported that s-BAFF levels are higher in patients with renal involvement.[11,15,23,27,44]

Neuropsychiatric manifestations are highly prevalent in SLE patients, while the cause and pathogenesis of brain damage are still elusive. Our findings indicate that u-BAFF was significantly higher in SLE patients with nervous involvement than those without nervous involvement. However, this was not the case for s-BAFF. Likewise, Vincent et al.[11] found that there is an association between increased BAFF levels and central nervous system (CNS) involvement. Conversely, according to George-Chandy et al.'s[45] study, the amount of local BAFF in the CNS and cerebrospinal fluid is valuable, whereas s-BAFF levels do not relate to CNS involvement. Recently, laboratory evidence indicates that intraventricular injection of IgG derived from SLE patients' sera into normal mice can activate the brain M1 microglia by increasing BAFF-induced expression.[46]

In terms of musculoskeletal, cutaneous, and hematologic manifestations, our results showed higher serum BAFF levels in lupus patients with cutaneous involvement compared to those without cutaneous manifestations. In line with our results, evidence shows that high levels of BAFF have been seen among lupus patients with musculoskeletal involvement.[23] In addition, higher BAFF levels have been reported in lupus patients with cutaneous lesions compared to healthy controls, further established by studies that observed local expression of BAFF rose significantly in patients with malar rash.[23,47,48] In evaluating the relationship between blood disorders and BAFF levels, results showed a predominance of lymphopenia and hypogammaglobulinemia with elevated BAFF levels.[23,44]

One of the critical limitations of this study was that the patients were not new cases and were under different lines of treatment; hence, receiving various drugs along with immunological changes due to disease progression could affect the results. Multivariate analysis with adjustment for confounders could have been conducted to assess the correlation between BAFF and SLEDAI-2K scores. In addition, only the serum and urine level of BAFF was investigated, and evaluating of the serum level of the BAFF receptor and its gene expression was not conducted, making it difficult to interpret the results. Therefore, we suggest that future studies consider BAFF gene expression in newly diagnosed SLE patients by measuring serum receptor concentration and its gene expression with periodic follow-up.

In conclusion, there is a significant positive correlation between the serum and urinary BAFF levels and SLE disease activity. Furthermore, significantly higher levels of s-BAFF and u-BAFF have been observed in patients with active lupus compared to inactive lupus and healthy subjects, indicating a possible role for BAFF in the pathogenesis of SLE disease activity.

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