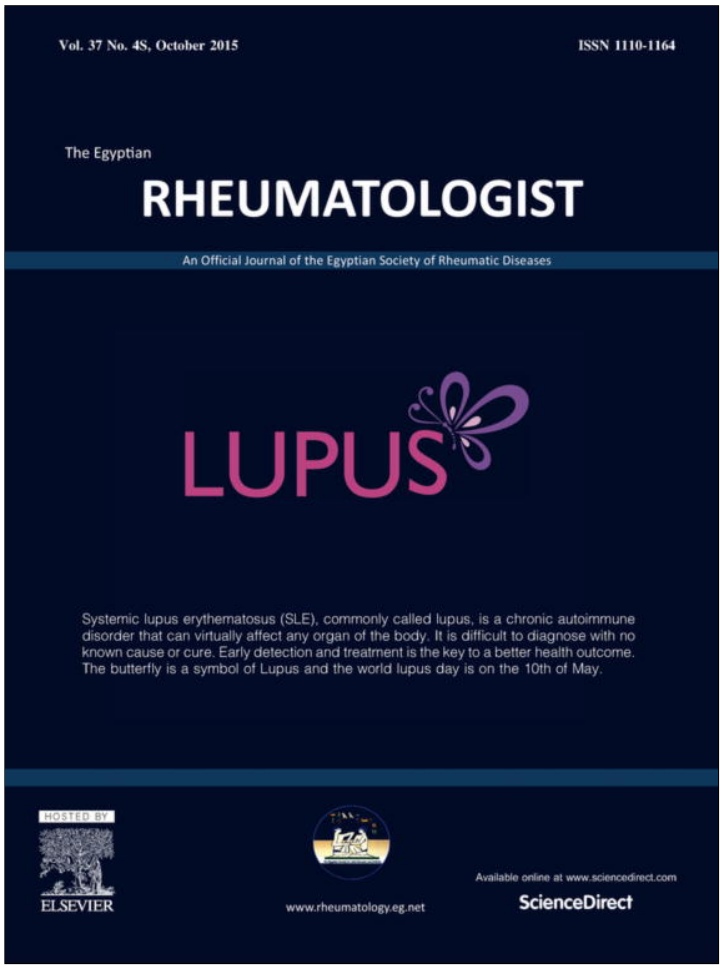

The Egyptian Rheumatologist (2015) 37, S19–S24

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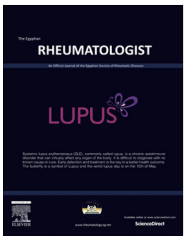

ORIGINAL ARTICLE

The neuropeptide adrenomedullin, could it be linked to renal involvement and disease activity in systemic lupus erythematosus?

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Received 31 May 2015; accepted 5 June 2015
Available online 11 July 2015

KEYWORDS

Adrenomedullin;
SLE;
Lupus nephritis;
Proteinuria;
Disease activity (SLEDAI)

Abstract *Aim of the work:* The aim of this study was to assess adrenomedullin level in systemic lupus erythematosus (SLE) patients with nephritis compared with those without and healthy controls and to correlate adrenomedullin level with SLE disease activity.

Patients and methods: Serum adrenomedullin was evaluated in 60 SLE patients (mean age 27.7 ± 8.25 years) and in 20 matched controls. The SLE patients were divided into two groups: Group I (with nephritis) and Group II (without) (30 patients each). The SLE disease activity index (SLEDAI) was assessed.

Results: The median serum adrenomedullin levels were significantly higher in SLE patients (7.4 ng/ml) compared to healthy controls (3.1 ng/ml) ($p < 0.001$). It showed a statistically significant difference between group I (8.8 ng/ml) and II (6.1 ng/ml) ($p < 0.01$). A significant relation was observed between the level of serum adrenomedullin with the neuropsychiatric manifestations ($p = 0.006$) and vasculitic lesions ($p = 0.014$) in group II patients and with pulmonary hypertension ($p = 0.04$), oral ulcers ($p = 0.03$), and serositis ($p = 0.02$) in group I. A significant negative correlation was found in group I patients between adrenomedullin and 24 h protein/day ($r = -0.38$, $p < 0.05$), as well as platelets & C4, and with C3 in group II as well as a highly significant correlation between SLEDAI and adrenomedullin level in SLE patients ($r = 0.76$, $p < 0.001$) and steroid dose ($p < 0.001$).

Conclusion: Serum AM is elevated in SLE especially in lupus nephritis patients & correlates with lupus disease activity. It is negatively associated with urine protein excretion per 24 h in the group of lupus nephritis patients. Serum AM may be considered among biological markers in SLE.

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Peer review under responsibility of Egyptian Society of Rheumatic Diseases.

http://dx.doi.org/10.1016/j.ejr.2015.06.004

1. Introduction

Lupus nephritis is one of the most severe forms of organ involvement in systemic lupus erythematosus (SLE) and occurs in at least 50% of patients [1]. Key factors play a considerable role in the pathogenesis of SLE as oxidative stress [2], apoptosis [3] and cytokine overproduction [4–7]. Current evidence suggests that dysregulated expression of cytokines plays a crucial role in the immunopathogenesis of SLE with a predominantly type 1 T-helper cell (Th1) activation in patients with active lupus nephritis [1].

A number of biochemical markers are currently used to clinically assess SLE renal disease activity, such as anti-double stranded deoxyribonucleic acid (ds-DNA) antibodies and complement component levels. Nevertheless, the correlation between these markers and lupus nephritis is imperfect, and their utility in reflecting disease activity remains controversial [8].

The importance of measuring vascular biomarkers as Adrenomedullin reflects the fact that the molecule is released by endothelial cells injury [9]. Adrenomedullin (AM) is a 52 amino acid peptide originally isolated from extracts of human pheochromocytoma tissue and it belongs to the calcitonin/calcitonin gene-related peptide (CGRP) family [10]. Pro-inflammatory cytokines especially interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α), which are pivotal in mediating the inflammatory process of SLE, appear to stimulate the production of AM in various cell types in SLE [11]. In lupus nephritis, the presence of IL-1, IL-6 and TNF-α in diseased kidney appears to mediate local pathogenic effects such as mesangial proliferation [12]. It has been shown that AM suppresses the secretion of pro-inflammatory cytokines such as TNF-α in macrophage cell line so that they can suppress mesangial cell mitogenesis [13]. Neuropeptides as AM can exhibit potent anti-inflammatory activities. They can regulate different critical levels of innate immunity [14]. The capacity of these neuropeptides to regulate adaptive immunity has been reported. They can impair activation/differentiation of Th1 cells [15].

The aim of this study was to assess adrenomedullin level in SLE patients with nephritis compared with those without and healthy controls, and to correlate its level with disease activity.

2. Patients and methods

Sixty SLE patients were recruited from the outpatient and inpatient units of Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University Hospitals, and were diagnosed according to American College of Rheumatology (ACR) revised criteria [16]. Twenty healthy subjects, matched for age and sex included in the study served as a control group. The patients were classified according to renal SLEDAI score into 2 groups; Group I comprised 30 SLE patients with lupus nephritis (having a renal SLEDAI of $\geqslant 8$; at least 2 abnormal results for renal parameters on at least two occasions) [17] and group II comprised 30 SLE patients without nephritis. The following conditions which may affect adrenomedullin levels were excluded; uncontrolled systemic hypertension: systolic blood pressure (SBP) > 140 mmHg ± diastolic blood pressure (DBP) > 90 mmHg, coronary heart disease or congestive heart failure, end-stage renal failure, pregnancy, chronic respiratory diseases, diabetes mellitus, chronic liver diseases. Informed consents were taken from the patients and the study was approved by the local ethics committee.

All the patients were subjected to full history taking, clinical examination and Disease activity assessment using the SLE disease activity index (SLEDAI) [18]; Mild activity (SLEDAI; 1–10), Moderate activity (SLEDAI; 11–20), High activity (SLEDAI; 21–45). Patients were subjected to laboratory investigations as follows: complete blood count (CBC), erythrocyte sedimentation rate (ESR), Liver and kidney functions, urine analysis, antinuclear antibodies (ANA), anti ds-DNA, complement C3 (normal value: 90–180 mg/dl) and C4 (normal value: 10–40 mg/dl) tests. Adrenomedullin level was tested in the sera of patients and controls using Enzyme Linked Immunosorbent Assay (ELISA).

2.1. Serum adrenomedullin measurement

Blood samples from patients and controls were centrifuged and stored at -80° C until assay of adrenomedullin. Sera were analyzed by ELISA according to the manufacturer's protocols (ELISA kit, Cat No: EIA-3418, Lot: 601777, DRG International Inc., USA).

Renal biopsy was performed in those patients with lupus nephritis and classified according to the world health organization (WHO) criteria [19].

Statistical analysis: Data obtained from the study were coded and entered using the software SPSS (Statistical package for social science) version 16.0. Quantitative parametric data were described in mean and standard deviation (SD), while non parametric data in median and percentiles. Percentages were used when appropriate. Comparison between groups was done using Chi square test for qualitative variables. For quantitative data, comparison between 2 groups was done by Mann–Whitney test for nonparametric data and among 3 groups by Kruskal Wallis test. The correlation between serum adrenomedullin level and other biochemical data and SLEDAI was assessed by Spearman coefficient of correlation. ROC curve was done to get the best cutoff to discriminate between SLE nephritis versus non-nephritis and control and also to get the best cutoff to discriminate between SLE patients with activity $\leqslant 10$ according to SLEDAI versus SLE patients with more active disease > 10. Interpretation of the area under the curve (AUC): 0.50–0.75 = fair, 0.75–0.92 = good, 0.92–0.97 = very good and 0.97–1.00 = excellent [20]. The p-value is considered significant if < 0.05.

3. Results

The SLE patients were 54 females (90%) and 6 males (10%), their ages ranged from 13 to 51 years with mean age of 27.75 ± 8.25 years. The disease duration in all patients ranged from 0.33 to 20 years with mean of 5.5 ± 4.5 years. The 20 matched control ages ranged from 16 to 40 years with a mean of 29 ± 6.13 years.

On comparing between group I and II SLE patients as regards the various demographic and clinical parameters, no significant difference was found apart from the SLEDAI score that was significantly higher in group I compared to group II

($p < 0.001$). Regarding the laboratory parameters, group I patients showed a significantly higher level of 24 h proteins ($p = 0.001$) and serum creatinine ($p = 0.03$) as well as a lower serum C3 ($p = 0.01$) compared to group II while no significant difference was observed in the other laboratory parameters between the two groups. The clinical and laboratory characteristics of the patients with and without nephritis are shown in Table 1.

Serum adrenomedullin level was comparable between adult ($n = 47$) and juvenile onset ($n = 17$ including 4 children) SLE patients ($p = 0.96$). However, the level tended to be lower in the children (8.5 ± 0.98 ng/dl) compared to the adult patients (9.26 ± 10.5 ng/dl) ($p = 0.6$).

The median level of serum adrenomedullin was significantly higher in the SLE patients (7.43 ng/ml) compared to the controls (6.1 ng/ml) and was higher in group I compared to group II patients (Table 2, Fig. 1). The best cutoff of adrenomedullin to discriminate between SLE nephritis versus SLE without nephritis and control was 6.8 ng/dl, with an area under the curve of 78% ($p < 0.001$, sensitivity 73% and specificity 78%) (Fig. 2). In group I patients, the serum adrenomedullin level in group I patients tended to be higher in class IV patients ($n = 7$) compared to those with other classes of renal biopsy (II,III,V) (23 patients) but with no significant statistical difference ($p = 0.84$).

A significant correlation was observed between the level of serum adrenomedullin with the neuropsychiatric manifestations ($p = 0.006$) and vasculitic lesions ($p = 0.01$) in group II patients and with pulmonary hypertension ($p = 0.04$), oral ulcers ($p = 0.03$), and serositis ($p = 0.02$) in group I. Otherwise there were no statistically significant correlations with the other clinical features.

The serum adrenomedullin in all SLE patients significantly correlated with the ESR ($p = 0.001$), anti ds-DNA ($p = 0.02$) and negatively with the hemoglobin content ($p = 0.005$), WBC count ($p = 0.01$), C3 ($p = 0.001$) and C4 ($p = 0.001$) levels. It is worth to mention that an insignificant correlation was found between adrenomedullin and 24 h urine protein in all SLE patients ($r = 0.19$, $p = 0.13$). A significant negative correlation was found with the platelets ($p = 0.01$), C4 ($p = 0.008$) and 24 h protein in urine ($p < 0.05$) (0.03) in group I, while with C3 ($p = 0.03$) in group II. Otherwise there were no statistically significant correlations with the other laboratory parameters.

A significant correlation was present between the serum adrenomedullin level in SLE patients and the SLEDAI ($r = 0.76$, $p < 0.001$). (Fig. 3). Moreover, a significant correlation of serum adrenomedullin and renal SLEDAI was present in group I patients ($r = 0.4$, $p = 0.02$). The best cutoff of adrenomedullin to discriminate between patients with SLEDAI ⩽

Table 1 The clinical and laboratory characteristics of the systemic lupus erythematosus patients with and without nephritis.

Variable	Systemic lupus erythematosus patients ($n = 60$)		
	Group I ($n = 30$)	Group II ($n = 30$)	*P*
Age (years)	28.3 ± 7.6 (13–48)	27.2 ± 8.9 (14–51)	0.58
Disease duration (years)	6.6 ± 4.8 (0.4–20)	4.4 ± 3.9 (0.3–20)	0.06
Gender F:M	25:5	29:1	0.64
SLEDAI	13.8 ± 7.1 (2–30)	7.4 ± 6.7 (2–27)	**<0.001**
Clinical manifestations			
Malar rash	17 (56.7)	18 (60)	0.36
Photosensitivity	13 (43.3)	11 (36.7)	0.34
Alopecia	12 (40)	6 (20)	0.19
Oral ulcers	12 (40)	13 (43.3)	0.09
Serositis	4 (13.3)	5 (16.7)	0.63
Arthritis	7 (23.3)	4 (13.3)	0.17
Neuropsychiatric	7 (23.3)	7 (23.3)	0.51
Vasculitis	3 (10)	3 (10)	0.15
Pulmonary hypertension	3 (10)	–	–
Laboratory feature			
ESR (mm/h)	45.2 ± 34.3 (5–130)	51.0 ± 31.7 (5–150)	0.49
Hb (g/dl)	11.3 ± 1.9 (7.7–14.4)	11.03 ± 1.9 (7–15)	0.68
WBCs ($\times 10^3/\mu L$)	7.2 ± 3.1 (2.7–14.2)	5.65 ± 2.9 (2.1–15.5)	0.05
Platelets ($\times 10^3/\mu L$)	257.6 ± 108.3 (67–571)	293.3 ± 103.9 (83–516)	0.19
Creatinine (mg/dl)	0.6 ± 0.2 (0.3–1.1)	0.5 ± 0.2 (0.1–0.9)	**0.03**
24hrs urine protein (g/d)	1.07 ± 1.3 (0–6.8)	0.12 ± 0.13 (0–0.5)	**<0.001**
Albumin (g/dl)	3.6 ± 0.7 (1.5–4.5)	3.8 ± 0.5 (3–4.9)	0.07
C3 (mg/dl)	74.6 ± 28.3 (22–130)	97.5 ± 32.2 (31.8–158)	**0.01**
C4 (mg/dl)	15.8 ± 11.1 (3–43.6)	18.8 ± 10.1 (3.77–45)	0.2
Positive ANA	30 (100)	30 (100)	–
Positive Anti-ds DNA	24 (80)	15 (50)	0.36

Group I: Lupus nephritis patients, Group II: patients without lupus nephritis, FM: female to male ratio, SLEDAI: SLE disease activity index, ESR: erythrocyte sedimentation rate, Hb: hemoglobin, WBC: white blood cells, C: complement, ANA: antinuclear antibody, Anti-ds DNA: double stranded DNA Results are presented as mean ± SD (range) or number (%). Bold values are significant at $p < 0.05$.

Table 2 Comparison of the median levels of serum adrenomedullin in systemic lupus erythematosus patients with (group I) and without nephritis (group II) and the control.

Serum adrenomedullin (ng/dl)	SLE patients (n = 60)		Control (n = 20)	p
	Group I (n = 30)	Group II (n = 30)		
Range	0.9–46.98	0.6–12	0.7–7.9	
Median	8.8	6.1	3.1	**< 0.001**
25–75th	5.8–11.6	2.5–7.8	0.9–5.1	

Group I: Lupus nephritis patients, Group II: patients without lupus nephritis. Bold values are significant at $p < 0.05$.

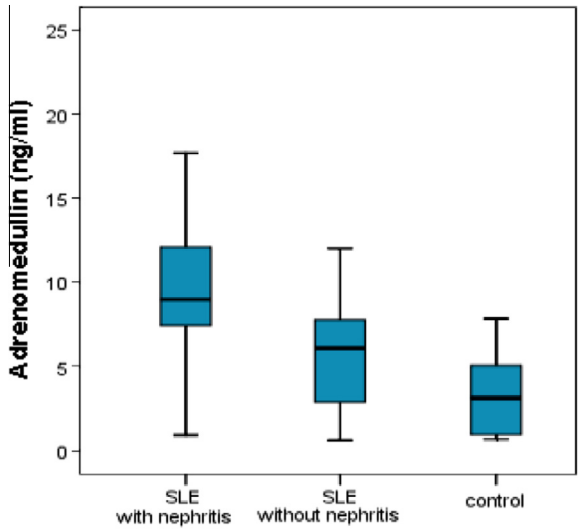

Figure 1 Boxplot showing serum adrenomedullin levels in systemic lupus erythematosus (SLE) patients with (group I) and without nephritis (group II) and control.

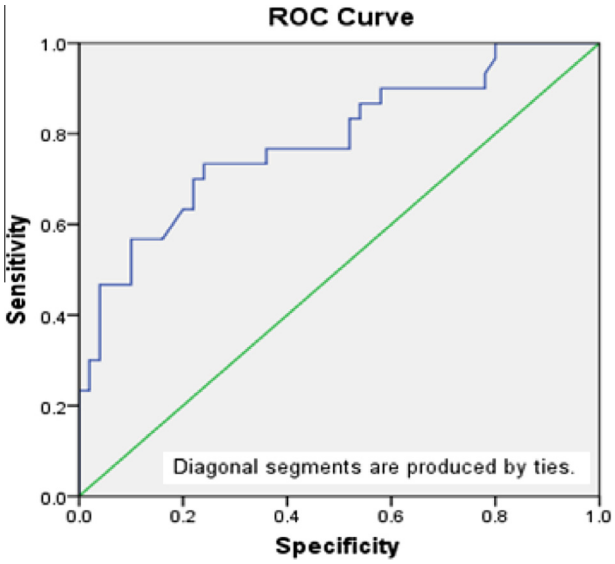

Figure 2 Receiver Operating Curve (ROC) analysis showing the diagnostic performance of serum adrenomedullin for discriminating systemic lupus erythematosus (SLE) patients with nephritis from those without.

10 versus those with more active disease (> 10) was 8.03 ng/dl with an area under the curve of 91.7% ($p < 0.001$, sensitivity 78.6% and specificity 96.9%) (Fig. 4).

All patients received steroids, cyclophosphamide by 20, antimalarials in 33, azathioprine in 29 and Mycophenolate mofetil in 5 patients. Only the steroid dose was significantly higher in group I vs II patients (23.1 ± 11.9 and 14.3 ± 12.7 mg/d respectively) ($p = 0.026$). A significant correlation was found between adrenomedullin and steroid dose ($p < 0.001$).

4. Discussion

Our study confirmed that serum adrenomedullin levels were significantly higher in SLE patients compared to healthy controls especially in patients with lupus nephritis. This agrees with the results of other studies [9,11,21].

In the present work, serum adrenomedullin showed a good diagnostic reliability in discriminating SLE patients with nephritis from those without (sensitivity 73%, specificity 78%, cut-off value 6.8 ng/dl). In support to our results, Kronenberg [22] reported that adrenomedullin showed greater specificity (87.3%) and good discriminative capability for patients who will experience progressive chronic kidney disease.

A non significant relation was found between the serum adrenomedullin level in lupus nephritis patients between class IV and other classes. This is supported by a previous study [11] that reported a similar behavior of adrenomedullin toward mesangial and glomerular cells regardless of the histological class of lupus nephritis.

In our study, relation of serum adrenomedullin level with clinical manifestations of SLE patients showed a significant correlation with the neuropsychiatric manifestations ($p < 0.01$) and vasculitic lesions ($p < 0.01$). This is comparable to the findings of Yilmaz and co-workers [23] who reported a threefold higher level of adrenomedullin in schizophrenic patients compared to the level in the controls. The significant relation with vasculitic lesions is in agreement with another study [24] that found an elevated adrenomedullin level in patients with active giant cell arteritis.

An insignificant correlation was found between adrenomedullin and 24 h urine protein in SLE patients. A significant negative correlation was present only in those with lupus nephritis. Similar results were reported by other authors [11] who demonstrated an inverse relationship between plasma adrenomedullin and proteinuria in SLE patients. This is supported by Plank et al. [25] who stated that exogenous

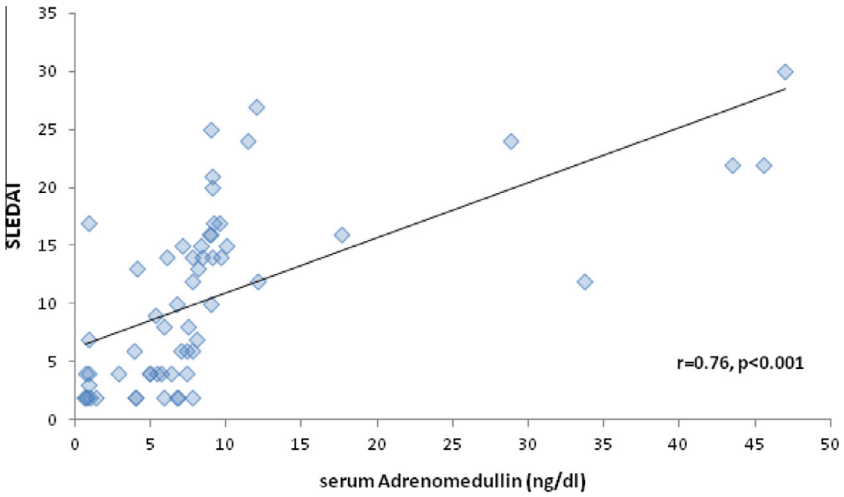

Figure 3 Correlation between adrenomedullin and systemic lupus erythematosus disease activity index (SLEDAI) in all SLE patients.

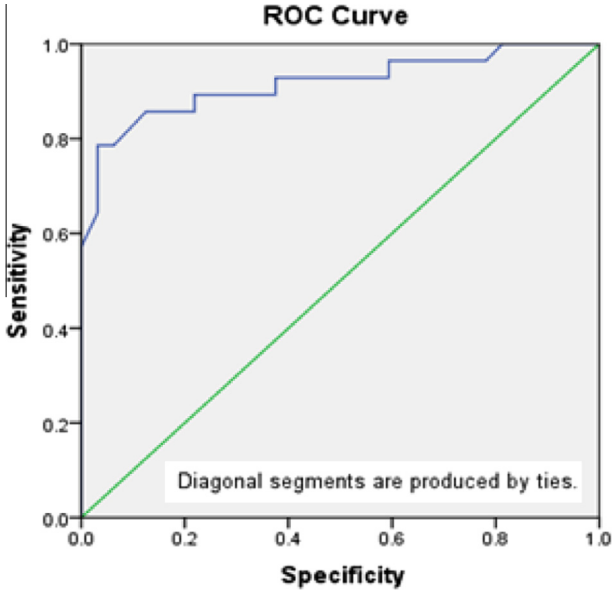

Figure 4 Receiver Operating Curve (ROC) analysis showing the diagnostic performance of serum adrenomedullin for discriminating systemic lupus erythematosus (SLE) patients with activity > 10 from those with mild activity.

adrenomedullin infusion reduces mesangial cell number and glomerular monocyte infiltration in the state of mesangial proliferation during acute mesangioproliferative glomerulonephritis and can influence its course.

This is further supported by a previous study [26] which showed that adrenomedullin could suppress the proliferation of rat glomerular mesangial cells, in addition it was found that [27] mesangial cells grown in primary culture synthesize adrenomedullin, which is stimulated by TNF-α, IL-1β and hypoxic conditions. Adrenomedullin increased cAMP levels in mesangial cells leading to inhibition of their proliferation, migration, reactive oxygen generation and macrophage infiltration. On the other hand in another study [9] they found a significant correlation between adrenomedullin and 24 h proteinuria in all lupus patients.

In our study a highly significant correlation was found between SLEDAI and serum adrenomedullin level in SLE patients. This coincides with the findings of previous studies [9,11,21]. Moreover, adrenomedullin significantly correlated with the renal SLEDAI score and this coincides with the results of Mak and co-workers [11].

In the present study, adrenomedullin significantly correlated with the steroid dose and this was confirmed by other studies [12,28,29]. In contrast, other authors [11] found no significant relation. They explained this finding by that; while corticosteroids may have a direct stimulatory effect on adrenomedullin production, any suppression of disease activity might result in decreased stimulation of adrenomedullin secretion.

There are several limitations with the current study. First, not all renal biopsies were taken during the period of serum adrenomedullin level measurement since they were performed for clinical indications rather than for research purposes. Second, it is a cross-sectional study and we were unable to correlate the serum adrenomedullin level with various clinical variables, before and after effective immunosuppressive treatment. A longitudinal study on a larger population is recommended and will undoubtedly augment the fidelity of the results.

In conclusion, it was confirmed that adrenomedullin is elevated in SLE especially in lupus nephritis patients, and correlated with lupus disease activity. Negative association was found between adrenomedullin and urine protein excretion per day in lupus nephritis patients.

Conflict of interest

None.

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