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Role of Regulated on Activation, Normal T-Cell Expressed and Secreted (RANTES) Protein in Systemic Lupus Erythematosus and Its Relation to Disease Activity

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SAS and RAN conceptualized the study, collected the data and wrote the manuscript. Author RAAN revised the manuscript. Author AME performed the biochemical tests in the study, and also revised the manuscript. All authors read and approved the final manuscript

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ABSTRACT

Background: The protein known as RANTES, or Regulated on Activation, Normal T-Cell Expressed and Secreted, belongs to the CC or B chemokine subfamily. Systemic lupus erythematosus (SLE) causes chronic and acute inflammatory processes by recruiting T lymphocytes, monocytes, and eosinophils to inflammation sites.

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Objectives: To evaluate RANTES's capacity to detect SLE, lupus nephritis, and its relationship to lupus activity.
Methods: This case- control research had 90 participants, including 30 healthy volunteers and 60 SLE patients. All individuals had a thorough clinical examination, extensive taking of history, and standard investigations. In the lupus nephritis groups, an immunological test and evaluation of disease activity using the systemic lupus erythematosus disease activity index (SLEDAI) score and renal SLEDAI(r-SLEDAI) were performed. For all groups, ELISA was used to measure the serum RANTES concentrations.
Results: The level of serum RANTES was substantially greater in SLE group than control group. ROC curve analysis demonstrated that serum RANTES predicted existence of SLE with a sensitivity of 91.67% and a specificity of 86.67%. No substantial variation was existed in serum level of RANTES among the active and inactive lupus individuals or between lupus nephritis and non-lupus nephritis groups. No substantial association existed among serum RANTES and c3, c4, urinary proteins, SLEDAI or r- SLEDAI scores.
Conclusion: Serum levels of RANTES are elevated in individuals with SLE suggesting that it can be a new effective biomarker for the diagnosis of systemic lupus disease. But we could not demonstrate significant relation to lupus nephritis or activity of the disease.

Keywords: Normal t-cell expressed and secreted protein; RANTES; systemic lupus erythematosus; SLE; disease activity.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic, chronic immune-mediated disorder that causes tissue damage and pathologic participation in numerous organs. It is defined by the generation of autoantibodies. Most inflammatory cells in afflicted organs are T lymphocytes, which likely play a significant role in the illness process, leading to the description of SLE as a disease of faulty T-cell censoring. It is characterized by sporadic flare-ups of the illness, and which is unpredictable [1]. Kidney is one of organs may be involved in this disease. It occurs in 30–50% of adult SLE [2]. It is a type of glomerulonephritis in which the glomeruli become inflamed, and it is the most serious complication of SLE and a predictor of bad prognosis. It may be present in the form of mild proteinuria or severe nephrotic syndrome, hematuria and may lead to in the end-to-end stage renal failure [3].

In addition to multiple investigations for SLE, there are important serum and urinary biomarkers of disease activity that because before the first symptom of a spike in serum creatinine was noticed, serious harm to the kidneys could have already taken place. Their value comes from the ability to distinguish between an acute flare and chronic damage, evaluate treatment response, and help doctors match an immune suppressive medicine more effectively to the demands of the patient and this will lead to decrease incidence of organs damage [1,4].

These markers include vascular endothelial growth factor (VEGF), soluble tumour necrosis factor receptor 1 (sTNF-R1), monocyte inhibiting protein 1a (MIP-1a), regulated on activation, normal T cell expressed and secreted (RANTES), and monocyte chemoattractant protein 1 (MCP-1) [5,6]. A tiny protein of 68 amino acids called RANTES, which stands for "RANTES," belongs to the chemokine subfamily or CC. The generation of Th-cell cytokines and leukocyte trafficking are both controlled by the C-C chemokine. Basophils, natural killer cells, eosinophils, dendritic cells, and mast cells are just a few of the cells that RANTES affects biologically. The lymphoid cells CD8+ and CD4+ T cells and monocytes are recruited to areas of inflammation by RANTES, which also causes leukocyte migration and activation [7]. By attracting T lymphocytes, monocytes, and eosinophils to the sites of inflammation, RANTES are thought to have a role in the pathophysiology and physiology of both chronic and acute inflammatory processes [8].

In the present study, we will investigate levels of serum RANTES in individuals with SLE and correlations to indexes of clinical laboratory and activity of the disease to determine their importance.

2. MATERIALS AND METHODS

Design: Cross- sectional study with case- control analytical component was conducted in Rheumatology unit, internal medicine department, Tanta University.

Participants: This study included 90 participants in 2 groups: study group included 60 SLE patients; control group included 30 healthy controls.

Criteria of inclusion: Individuals who were identified as having SLE in accordance with the SLICC diagnostic criteria for SLE [9].

Criteria of exclusion: Individuals suffering from any of the subsequent conditions were excluded from the investigation: pregnancies, diabetics, kidney disease that is end-stage, and malignancy and individuals who were diagnosed as Overlap syndrome or mixed connective tissue disease.

Sample size: The G-power software with was used to compute sampling size. Ninety participants were included, with an error of 0.05 and an 80% power according to population size in a previous study.

2.1 Methods

Everyone involved underwent to comprehensive taking of history, comprehensive physical examination, and lab tests such as complete blood count, c- reactive protein (CRP), renal function test, liver function test, Erythrocyte sedimentation rate (ESR), urinalysis, 24- hour urinary protein, Anti double-stranded DNA (anti-dsDNA), Antinuclear antibodies (ANA), C3, C4 levels, thrombophilia (lupus anticoagulant, anticardiolipin IgG & IgM). Individuals with renal insult had a kidney biopsy (proteinuria more than 500 mg/ day; rise of s. creatinine). 10 cm of venous blood samples were withdrawn under complete aseptic technique from all patients then immediately centrifuged and the serum was divided for routine investigations and virology. Routine Laboratory investigations were done using:

- Konilab Automated chemistry analyzer.
- CBC by ERMA cell counter.
- Auto immune markers (ANA, Anti ds DNA, C3, and C4) were performed by utilizing ELISA technique.

Serum RANTES level was estimated using ELISA Kits.

2.2 Statistical Analysis

In an SPSS sheet 20 tabulation, all data were compiled. To compare categorical information, Fisher's exact test and the chi-square test were also utilized. For comparing continuously distributed information with normal distribution, the student t-test was utilized. Unusually distributed data were compared using the Mann Whitney test. The Spearman technique was used to examine correlations between quantitative information. Utilizing receiver operating characteristics analysis (ROC), the cutoff point and specificity as well as sensitivity were detected.

3. RESULTS

There were 60 participants with SLE in the study, ranging in age from 16 to 65 and female predominance ((88.3%). The patients had disease duration ranged from 0.08 to 17 years. SLE patients were classified according to SELEDAI. 53.3% of people suffered a mild illness, 23% suffered a moderate illness, and 10% suffered a severe illness. Renal SELEDAI score was calculated also and 61.7% had active renal disease. ANA was positive in 88.3% of patients with SLE, Anti- dsDNA was positive in 91.7% of participants. Lupus anticoagulant was positive in 50% of patients while anticardiolipin was positive in 36.7% of patients. Mean values of C3 and C4 were 79.92 ± 28.21 and 16.78 ± 9.59 respectively. Diagnosis of lupus nephritis was made in 21 patients (existence of proteinuria more than 0.5 g/ day or rise of s. creatinine. Fifteen patients underwent renal biopsy and most of participants were diagnosed as LN class IV (33.3%); LN class II and class III were diagnosed in 14.3% of patients for each class. Class IV to V was diagnosed in 1 patient Also, class VI was present in 1 case (Table 1).

Thirty healthy controls were compared to lupus patients. Concerning age, and marital status, no statistically substantial variation was existed among the two groups. Regarding laboratory findings, hemoglobin mean values were higher among SLE group with statistically significant difference in comparison to healthy control group (SLE vs. control: 13.9 ± 2.18 vs. 12.1 ± 0.94; $p< 0.001$). Platelet count was lower with statistically substantial difference across group of SLE when compared to group of control (SLE vs. control "median": 0.23 vs. 0.29 $\times 10^3/\mu l$; $p= 0.002$). Both groups were comparable regarding blood urea, creatinine, hepatic aminotransferases, fasting blood glucose and ESR (Table 2). RANTES levels were measured in both SLE and control groups. Median, interquartile ranges were higher among SLE group (640; 527- 725) in comparison to healthy group (367.5; 269.9- 412.5; p< 0.001) (Fig. 1).

Table 1. Characteristics of SLE patients

	Total cohort (n= 60)
Sex No. (%)	
- Male	7 (11.7%)
- Female	53 (88.3%)
Age (years) Mean ± SD	33.28 ± 10.72
Disease duration (years) Median (IQR)	4.0 (1.0 – 7.5)
SELEDAI No. (%)	
- No (<4)	8 (13.3%)
- Mild (4- 8)	32 (53.3%)
- Moderate (8- 12)	14 (23.3%)
- Severe (>12)	6 (10%)
Renal SELEDAI No. (%)	
- Inactive (< 4).	23 (38.3%)
- Active (≥4)	37 (61.7%)
Lupus nephritis No. (%)	
- No	39 (65%)
- Inactive lupus nephritis	5 (23.8%)
- Active lupus nephritis	16 (76.2%)
Renal biopsy results No. (%)	
- II	3 (14.3%)
- III	3 (14.3%)
- IV	7 (33.3%)
- IV + V	1 (4.8%)
- VI	1 (4.8%)
- Undetermined	6 (28.6%)
ANA No. (%)	53 (88.3%)
Anti- dsDNA No. (%)	55 (91.7%)
Lupus anticoagulant No. (%)	30 (50%)
Anti- cardiolipin No. (%)	22 (36.7%)
C3 Mean ± SD	79.92 ± 28.21
C4 Mean ± SD	16.78 ± 9.59
C- reactive protein No. (%)	29 (48.3%)

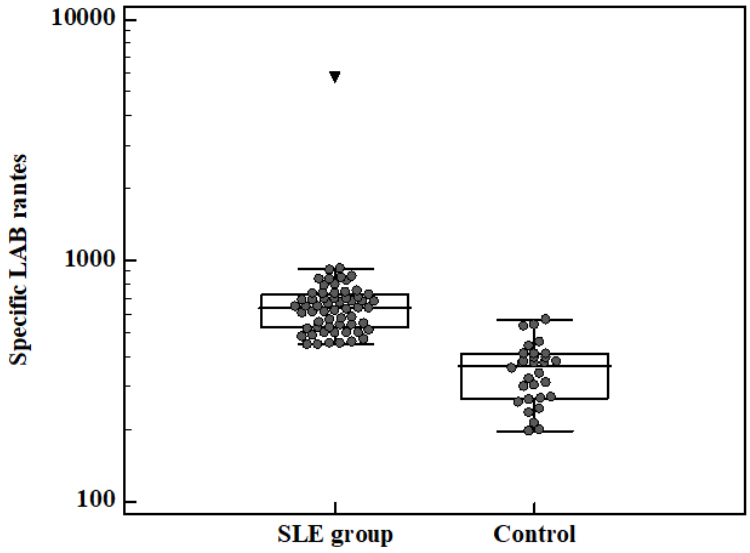

Fig. 1. Comparison between the two studied groups according to serum RANTES level

Table 2. Comparison between SLE and control groups

	SLE group (no= 60)	Control group (n= 30)	Test of significance	P value
Sex No. (%)			χ^2= 0.433	0.53
- Male	7 (11.7%)	5 (16.7%)		
- Female	53 (88.3%)	25 (83.3%)		
Age (years) Mean ± SD	33.28 ± 10.72	35.80 ± 10.23	t= 1.066	0.29
Hemoglobin (g/ dL) Mean ± SD	13.90 ± 2.18	12.10 ± 0.94	t= 4.951*	***<0.001****
White blood cells (×10³/µl) Mean ± SD	6.75 ± 2.59	7.32 ± 1.84	t= 1.205*	0.232
Platelets (×10³/µl) Median (IQR)	0.23 (0.17 – 0.30)	0.29 (0.25 – 0.34)	U= 535.0*	***0.002****
Blood urea (mg/dL) Median (IQR)	35.0 (29.0 – 45.0)	34.0 (29.0 – 41.0)	U= 749.0	0.196
S. creatinine (mg/dL) Median (IQR)	0.9 (0.73 – 1.1)	0.90 (0.80 – 1.2)	U= 824.0	0.512
Alanine aminotransferase IU/L) Median (IQR)	18.0 (15.0 – 37.0)	18.0 (15.0 – 25.0)	U= 878.0	0.850
Aspartate aminotransferase IU/L) Median (IQR)	23.0 (17.50 – 32.0)	24.50 (19.0 – 30.0)	U= 890.0	0.935
Fasting blood glucose (g/dL) Mean ± SD	100.1 ± 16.11	101.6 ± 16.68	t= 0.425	0.675
ESR Median (IQR)	51.5 (35.0 – 90.5)	8.0 (6.0 – 12.0)	U= 32.0*	***<0.001****
RANTES Median (IQR)	640 (527.0- 725.2)	367.5 (269.8- 412.5)	U= 60.0*	***<0.001****

*(χ^2) Chi- square test; (t) Student t- test; (U) Mann Whitney test; *Level of significance < 0.05*

Table 3. Differences between SLE subgroups regarding RANTES

		Test of significance	P value
SELEDAI		H= 1.989	0.575
- No (<4) (n= 8)	653.4 (446.9- 852.5)		
- Mild (4- 8) (n= 32)	627.2 (452.1- 5782.1)		
- Moderate (8- 12) (n= 14)	685.5 (470.1- 930.8)		
- Severe (>12) (n= 6)	629.8 (484.7- 860.6)		
Lupus nephritis		U= 341.0	0.288
- No (n= 39)	624.1 (446.9- 852.5)		
- Yes (n= 21)	657.9 (470.1- 5782.1)		
Renal SELEDAI		U= 375.0	0.443
- Inactive (< 4) (n= 23)	643.8 (446.9- 5782.1)		
- Active (>4) (n= 37)	630.3 (452.1- 930.8)		

*(H) Kruskal- Wallis test; (U) Mann Whitney test; *Level of significance < 0.05*

Table 4. Correlation between serum RANTES level and different parameters

	Serum RANTES level	
	r_s	p
Disease duration (years)	-0.021	0.872
SELEDAI	0.040	0.760
Renal SELEDAI	-0.036	0.786
C3	0.018	0.892
C4	0.129	0.327
Urinary protein	0.017	0.895

r_s: Spearman coefficient

Table 5. Validity (AUC, sensitivity, specificity) for serum RANTES level to discriminate SLE group patients (n = 60) from control (n = 30)

	AUC	p	95% CI	Cut off	Sensitivity	Specificity	PPV	NPV
Serum RANTES level	0.967	<0.001*	0.931 – 1.0	>458	91.67	86.67	93.2	83.9

AUC: Area Under a Curve *p value: Probability value*
CI: Confidence Intervals
NPV: Negative predictive value *PPV: Positive predictive value*
**: Statistically significant at p ≤ 0.05*

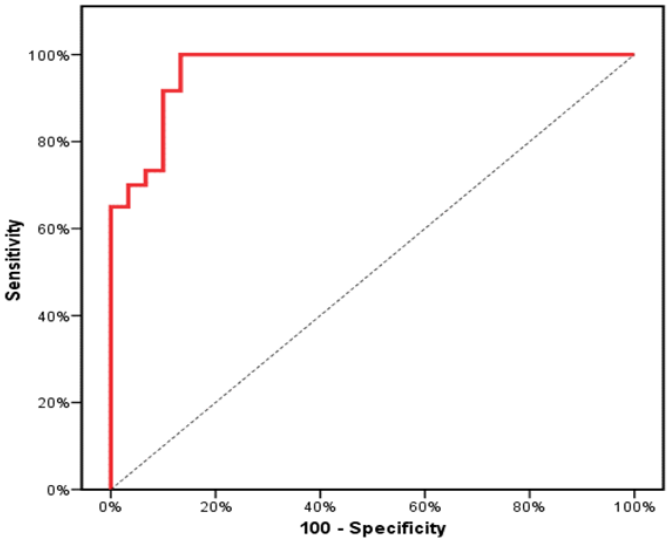

Fig. 2. ROC curve for serum RANTES level to discriminate SLE group patients (n = 60) from control (n = 30)

Lupus patients were divided according to SELEDAI into, no activity, mild, moderate, and severely active disease. The 4 groups had comparable expression of RANTES with no statistically significant difference. When dividing SLE patients according to presence of lupus nephritis or not, no statistically substantial variation was existed among the two groups regarding RANTES levels. According to Renal SELEDAI, participants were categorized into active and inactive with no statistically substantial variation among the two groups regarding RANTES levels (Table 3). no statistically substantial association was existed among RANTES levels and disease duration, SELEDAI, R. SELEDAI, C3, C4 and 24- hour urinary protein (Table 4). At cutoff value equal to >458 ng/L, RANTES had 91.67% sensitivity and 86.67% specificity in diagnosis of SLE (Table 5).

4. DISCUSSION

In the current investigation, we examined serum RANTES levels in individuals with SLE and their

relationships to clinical laboratory indices and disease activity to assess their importance and get a better knowledge of RANTES in SLE. We studied 30 healthy controls and 60 individuals with SLE who did varying levels of exercise in order to accomplish this goal. Each patient had a comprehensive physical examination and were sampled for variable laboratory investigations including serum RANTES. Patients were recruited from Tanta university hospitals.

The included patients had female predominance with age ranged from 16 to 65 years. Both groups were matched in age and sex per selection criteria of the control group. The female predominance of SLE had reported in many studies [10-12].

A study by Touma et al., reported high sensitivity and specificity of SELDAI in prediction of SLE activity. In the current study, we used SELDAI to predict disease activity and we found that 53.3% of the included patients suffered mild illness activity, 23.3% suffered moderate illness activity and 10 suffered severely active illness [13]. Renal-SELDAI (R. SELDAI) was used in the current study. R. SELDAI validity in participants with lupus nephritis were also approved in previous studies and was found to be correlated well with changes in serum creatinine and proteinuria and had been used in clinical studies [14-16].

A statistically substantial variation was existed among the two groups regarding hemoglobin levels as mean values of hemoglobin were lower among SLE group with statistically significant difference. This is comparable to what has been stated by Akca et al. [17]. He reported existence of anemia at diagnosis time in 79% of the included SLE patients. Gulay and Dans, stated anemia as the most prevalent hematological abnormality in pediatric individuals with SLE [18]. On the other hand, few SLE cases with polycythemia were reported and it was referred to presence of another autoimmune diseases and some polycythemia patients were presented with SLE like manifestations [19]. Both groups were comparable regarding white blood cell count. In contrary to our study, leucopenia was reported to be the 2nd commonest hematologic manifestations [17,20]. Platelets had lower median and quartile ranges among SLE patients than control group in the current study with statistically significant difference. This comes in hand with other studies [17,21]**.** They explained their findings by presence of auto splenectomy or hyposplenism.

In the current study, serum creatinine and blood urea values were greater among SLE group than control group. This comes in hand with the selection criteria of the control group being healthy and the SLE group included patients with renal affection. Renal affection in SLE is reflected by proteinuria and/or increased serum creatinine which is accompanied by increased blood urea [22,23]**.**

ESR was higher with statistically substantial difference across SLE group than control group. This is in accordance with other studies who reported that increased ESR was independent predictor of activity index of renal biopsies in lupus nephritis patients [24,25]**.** No statistically substantial variation was existed among both groups concerning CRP. Similarly, some studies stated no variation among SLE and controls regarding CRP [26,27]**.** This is against what was reported in other studies [28,29].

In the present study, lupus nephritis diagnosis was made in 35% of the included patients and it is lower prevalence rate among SLE patients than what was stated in other studies [30,31], this can be explained by limited number of collected LN patients. They reported 40-60% incidence of lupus nephritis among SLE patients. Renal SELDAI was used to determine degree of lupus nephritis activity and participants were categorized into 2 groups (inactive<4 and active ≥4). *Vila et al.,* reported renal affection in 11.3% of lupus cases. Most of patients had lupus nephritis class IV (33.33%) while the other classes had variable distribution and class V had the lowest prevalence (4.8%) [32]. This comes in hand with lupus nephritis classes distribution in research by Al Arfaj et al., [33].

All patients in both groups were tested for serum *RANTES* and it was higher with statistically significant difference among SLE patients than control group. In general, chemokines were reported to be increased with SLE [34]. This comes in hand with a study by Lu et al., who found RANTES levels were higher significantly among SLE patients SLE: control; 16.26 ± 4.37 µg/ml; p<0.001) [35]. This suggested that the inflammatory response in SLE may be brought on by an increase in the proinflammatory cytokine RANTES. MIP-1 and RANTES levels in serum were observed to be greater in individuals with SLE than in control persons by Vila et al., [32]. The concentrations of the chemokines MCP-1, MIP-1β, SDF-1α, IP-10, and RANTES were reported to be considerably

higher in SLE patients in contrast to controls by Eriksson et al., & Meller et al., [36,37]. Zhao et al., reported that in SLE, there is decrease of micro-RNA which negatively correlated with RANTES expression and this explains the increased RANTES expression among SLE patients [38]. In contrast, Ye et al., & Lima et al., did not found a correlation between RANTES genotypes and SLE as the distribution of RANTES' genotypes and alleles were comparable to healthy controls [7,8]. We did not study the different gene polymorphisms of RANTES and also there was genetic variability between the included populations in different studies and this may explain the difference between the current study and these studies. Our participants were categorized into 4 groups as regard to SELDAI to detect activity of the disease. All groups were comparable regarding serum RANTES which reflects that serum RANTES could not predict disease activity. This comes in hand with other studies [32,35].

In the present study, there was no association among incidence of lupus nephritis and expression of RANTES. This comes in hand with Vila et al., & Lu et al., [32,35]. On the other hand, a number of studies have linked lupus nephritis to chemokines, notably MCP-1 and RANTES [8, 39]. Chan et al., stated that urinary RANTES but not serum increased significantly among lupus nephritis patients [40]. *Tian et al.,* reported strong association between urinary RANTES and flare of lupus nephritis [41]. Investigations have reported that Participants with active lupus nephritis had considerably higher levels of RNATES mRNA expression in their urine sediment [42]. no substantial association was existed among RANTES and C3, C4 or duration of the disease in the current study. This is against what was reported by Lu et al., [35]. In spite that he found a correlation between C3, C4 and RANTES, he failed to find significant association with activity of the disease.

The work had the advantage of being performed on patients with variable disease activity. It also tested the correlation between RANTES with lupus nephritis and the correlation between RANTES and different activity markers. In this work, we tested for the initial time the accuracy of RANTES in diagnosis of SLE.

5. CONCLUSION

In conclusion, our study present evidence that serum RANTES is a promising non- invasive biomarker for SLE that can be used as an adjunctive laboratory measure to detect SLE.

6. LIMITATIONS

The study had some limitations as lack of randomization. We also did not include other chemokines which were known to have a correlation with SLE, and this affects the specificity of RANTES. We did not evaluate the effect of different treatment modalities on RANTES expression.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available as MS Excel files (.xlsx) from the corresponding author upon reasonable request.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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