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Angiotensin-converting enzyme (ACE) serum levels and gene polymorphism in Egyptian patients with systemic lupus erythematosus

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Objectives: to investigate the association of angiotensin-converting enzyme (ACE) gene polymorphism and serum ACE level among Egyptian SLE patients and its relation to disease activity parameters. **Subjects and methods:** we enrolled 50 Egyptian female systemic lupus erythematosus (SLE) patients and 29 healthy controls. Measurement of serum ACE level was done using ELISA, and the ACE genotype was determined by polymerase chain reaction using genomic DNA from peripheral blood. **Results:** a significant difference was found in ACE genotypes between SLE patients and controls ($\chi^2 = 7.84$, $p = 0.02$). The frequency of ACE DD versus (DI and II) genotypes was significantly higher in SLE patients compared with controls ($\chi^2 = 5.57$, $p = 0.018$ and OR for risk of SLE was 3.1 with 95% confidence interval: 1.198.06). Mean serum ACE level was significantly higher in the SLE group compared with controls ($p = 0.006$). Subjects with DD genotype had a significantly higher mean level than those with DI ($p = 0.015$) and II genotypes ($p = 0.02$). Lupus nephritis patients had a significantly higher frequency of DD versus DI and II genotypes compared with lupus patients without nephritis (Fisher's exact test, $p = 0.025$) and controls ($\chi^2 = 8.74$, $p = 0.003$). SLE patients with vasculopathy had a significantly higher frequency of DD versus DI/II genotypes compared with SLE patients without vasculopathy (Fisher's exact test, $p = 0.04$) and controls ($\chi^2 = 9.84$ and $p = 0.002$). Mean serum ACE level was significantly higher in the lupus nephritis and SLE patients with vasculopathy compared with controls ($p = 0.008$, $p = 0.001$, respectively). Significant positive correlations were found between serum ACE level and serum creatinine and 24 h proteinuria ($p = 0.03$, 0.009, respectively). SLE patients with DD genotype had a statistically significant higher mean SLEDAI score than those with (DI/II) genotypes ($p = 0.02$). Significant positive correlation was found between serum ACE levels and SLEDAI scores ($p = 0.04$). **Conclusion:** ACE genotype and subsequently serum ACE level could be associated with the disease activity of Egyptian SLE patients; in addition, ACE deletion polymorphism might be used as one of the predictive factors for the activity of SLE. Further studies on a larger number of patients should be done to determine the exact prevalence of ACE gene polymorphism among Egyptian SLE patients. *Lupus* (2012) **21,** 103–110.

Key words: ACE *I*/*D* gene polymorphism; lupus nephritis; serum ACE level; SLE; SLEDAI; vasculopathy

Introduction

SLE is a complex autoimmune disorder involving environmental, genetic and hormonal elements. Due to the complexity and diversity of this disease, it appears that SLE will involve multiple genes interacting in a number of complicated ways. A number of genetic association studies have identified various candidate lupus susceptibility genes. These include members of the HLA family, complement genes, mannose-binding protein, Fcγ receptors, IL-10 and angiotensin-converting enzyme (ACE).[1]

ACE is expressed in a wide range of tissues including lung, endothelium, kidney, heart and testes. ACE plays a major role in the renin–angiotensin system (RAS), as it activates angiotensin I into angiotensin II by its metalloproteinase enzymatic activity and inactivates

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bradykinin via the kallikrein–kininogen system potentially resulting in decreased tissue perfusion.[1]

Angiotensin II (AII), the main effector molecule of the RAS, is a pleiotropic molecule and strong candidate for a mediator of the development and progression of renal disease in SLE. AII is a vasoactive peptide and growth factor that contributes to vascular reactivity, tissue remodeling and fibrosis.[2,3] AII is also a potent pro-inflammatory modulator with the ability to augment and perpetuate immune responses in renal and non-renal tissues.[4,5]

Specifically in the kidney, AII stimulates mononuclear cells, favoring hyperplasia and hypertrophy of mesangial, tubular cells and interstitial fibroblasts, and also increases expression and synthesis of the extracellular protein matrix leading to tissue fibrosis.[6] In the vascular wall, AII induces inflammatory changes in both the endothelial and vascular smooth muscle cells. AII increases smooth muscle cell contraction and affects smooth muscle proliferation, monocyte adhesion, platelet adhesion and aggregation.[7,8]

ACE gene is located on the long arm of chromosome 17q23 and shows characteristic polymorphism based on the presence (insertion [*I*]) or absence (deletion [*D*]) of a 287-base-pair (bp) long Alu repeat sequence of DNA within intron 16 which results in three possible genotypes (*DD* and II homozygotes, and *ID* heterozygotes).[9,10]

Studies have shown that the ACE insertion/deletion polymorphism, which relates to the amount of circulating enzyme within individuals homozygous for the deletion, has approximately two-fold higher tissue and plasma levels of ACE as compared with individuals homozygous for the insertion.[10,11]

ACE plays an integral role in the regulatory system responsible for endothelial control and vascular tone, systems that are commonly affected in lupus patients. Thus, it seems possible that ACE insertion/deletion may play a role in SLE, which can include vasculitis and vascular changes.[1]

Our goal was to explore the association between ACE insertion/deletion gene polymorphism and serum ACE level in Egyptian SLE patients, and whether they are correlated to the clinical parameters of SLE, especially lupus nephritis, vasculopathy and SLEDAI score.

Patients and methods

Study population

The study enrolled 50 Egyptian SLE female patients, fulfilling the 1982 revised criteria of the American Rheumatism Association for the classification of SLE,[12] with a mean age of 31.3 ± 6.5 years and mean disease duration of 4.3 ± 1.4 years, in addition to 29 healthy controls matched for age and sex with a mean age of 30.4 ± 7.1 years. All subjects were informed about the aim of the study and gave their consent. Out of the 50 SLE patients 17 had evidence of vasculopathy in the form of Raynaud's phenomenon and cutaneous vasculitis presented by palpable purpura, papules and plaques. None of the patients had evidence of either arterial or venous thrombosis; hypertension was found in six patients. Forty-two patients had hematological abnormalities, anemia was present in 30 patients (71%), while leucopenia was present in 20 patients (47.6%) and thrombocytopenia in 16 patients (38%). Thirty-five patients had nephropathy [persistent 24-h proteinuria > 0.5 g and/or active sediment (cellular casts-red cell, granular, tubular or mixed) and/or serum creatinine > 1.2 mg/dl and/or renal biopsy evidence of lupus nephritis (immune complex deposition)]. The histologic findings in renal biopsy specimens (obtained before starting treatment) were classified according to WHO criteriaminimal changes (class I), mesangial alterations (class II), focal proliferative (class III), diffuse proliferative (class IV), and membranous (class V) glomerulonephritis.[13] Fifteen patients without clinical evidence of nephropathy (no abnormalities in the urine test and serum creatinine ≤ 1.2 mg/dl). Significant weight loss ($> 10\%$) was found in 15% of the patients at initial presentation. Patients who were diabetic, those with a diagnosis of overlap syndrome (coexistence of lupus with other connective tissue diseases) and those undergoing hemodialysis or with a history of renal transplantation, were excluded from our study. All SLE patients were subjected to full history taking, general examination, cardiopulmonary, abdominal, neurological and locomotor systems examination. Systemic hypertension was recorded when systolic ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured in multiple occasions or when antihypertensive medication was taken. Routine laboratory investigations (complete blood count, liver and kidney functions by Jaffe kinetic method, and urine analysis), immunological assays (ANA and anti-DNA) were done by indirect immunofluorescence and serum C3 and C4 levels by nephelometry (Beckman, USA). Twenty-four hour urine samples were collected to estimate total urinary protein levels by the colorimetric method. Blood and urine samples were always collected on the same day.

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The global disease activity was assessed by SLEDAI.[14] All patients were taking steroids (dose range 15–50 mg/day), 45 patients on hydroxychloroquine (dose range 200–400 mg/day), 25 patients on azathioprine (dose range 100–150 mg/day) and 30 patients were receiving monthly cyclophosphamide pulse therapy depending on extent of renal lesion (dose range 700–1000 mg). Four patients with lupus nephritis (LN) and two lupus patients were taking angiotensin converting enzyme inhibitors or angiotensin receptor blocker (Arb).

The control subjects were unrelated to patients in the study but had similar social conditions and ethnic background to the patients. They have normal physical examinations, blood pressure < 135/85 mmHg, no abnormalities in urine and did not have a history of autoimmune or rheumatic diseases, or other diseases with a known genetic or hereditary predisposition. Serum ACE level was measured for included subjects in this study by ELISA using kit supplied by BEN (Biochemical Enterprise S.r.l., Milan, Italy).

ACE genotype determination

DNA was extracted from peripheral leukocytes by salting out technique[15] using reagents supplied by Sigma (Sigma Chemical Co., St Louis, MO, USA). The ACE gene I/D polymorphism were ascertained by polymerase chain reaction (PCR) employing oligonucleotides: forward (5'-CTGGAGAACC ACTCCCATCCTTTCT-3') and reverse (5'-GATG TGGCCATCACATTCGTCA GAT-3'), the primers, master mixture and restriction enzymes were supplied by Fermentes International Inc. (Burlington, Ontario, Canada). The PCR was carried out in a total volume of 25 µl containing 2.5 µl of genomic DNA, 1 µl (30 pmol) of each primer, 12.5 µl of master mixture [200 µM each of deoxyadenosine triphosphate (d-ATP), deoxycytidine triphosphate (d-CTP), deoxyguanosine triphosphate (d-GTP) and deoxythymidine triphosphate (d-TTP), in 1.5 mM magnesium chloride; 10 mM Tris-HCL; 50 mM potassium chloride, 0.1% Triton X-100 and 1.0 unit of Taq polymerase] and 8 µl of sterilized distilled water. The PCR reactions began with denaturation at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 1 min, annealing at 58°C for 1 min, extension at 72°C for 2 min, with a final extension at 72°C for 10 min. Enzymatic amplification was performed by PCR using Hybaid thermal cycler supplied by Promega Corporation (Promega Corporation, Madison, WI, USA). The PCR products (190 and 490 bp) were electrophoresed on ethidium bromide staining using gel electrophoresis apparatus supplied by Promega Corporation (USA) and visualized under UV transillumination. On electrophoresis, ACE genotype II showed a 490 bp band, genotype DD showed a 190 bp and genotype ID showed both 490 and 190 bp bands as represented in Figure 1.

Statistical analysis

The results were analyzed using SPSS computer software package, version 10.0 (Chicago, IL, USA). Qualitative data were presented in the form of number and percentage. Quantitative data were presented in the form of mean, SD and range when data were normally distributed. Student's t and one-way ANOVA tests were used for comparing two and more than two groups, respectively. Z test was done to compare genotype and allele frequencies. Differences in genotype and allele frequencies were evaluated by χ^2 or Fisher's exact tests. Odds ratio (OR) and 95% confidence interval (CI) values were calculated. A probability level (p) < 0.05 was considered significant.

Results

Characteristics of the included patients

Fifty female SLE patients were evaluated in this study; 35 had nephropathy and 15 patients had no clinical evidence of nephropathy. The main demographic and clinical features of the studied SLE patients are shown in Table 1.

ACE enzyme level and I/D gene polymorphism in SLE patients and control groups

The frequency of ACE DD versus (DI and II) genotypes was significantly higher in SLE patients

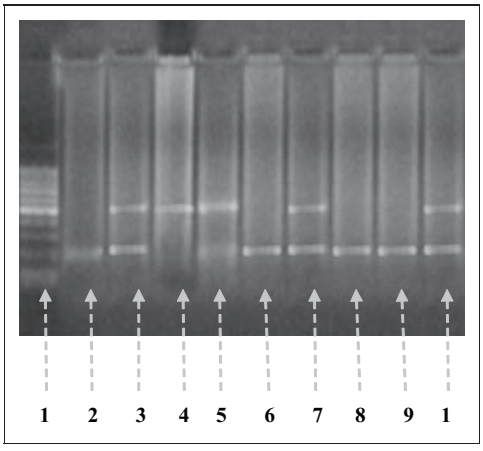

Figure 1 Results of PCR analysis of ACE gene polymorphism. DNA ladder: lane 1; DD genotype: lanes 2, 6, 8, 9; ID genotype: lanes 3, 5, 7,10; II genotype: lane 4.

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compared with controls ($\chi^2 = 5.57$, $p = 0.018$ and OR for risk of SLE was 3.1 with 95% CI: 1.19–8.06).

Mean serum ACE level was significantly higher in the SLE group compared with controls (40.03 ± 14.91 *vs.* 30.56 ± 12.44, respectively, $p = 0.006$), as shown in Table 2. There was a significant difference in mean ACE serum levels in relation to genotypes of the study population ($p = 0.008$), subjects with DD genotype had significantly higher mean level than those with DI (39.73 ± 13.15 *vs.* 32.02 ± 14.04 U/L, $p = 0.015$) and II genotypes (39.73 ± 13.15 *vs.* 16.95 ± 1.06 U/L, p = 0.02).

As shown in Table 3, LN patients had significantly higher frequency of DD versus DI and II genotypes compared with lupus patients without nephritis (Fisher's exact test, $p = 0.025$) and controls ($\chi^2 = 8.74$, $p = 0.003$). The OR for the risk of nephropathy in LN patients with ACE DD versus (DI and II) compared with lupus patients without nephritis and controls was 3.75 (95% CI: 1.1–13.31) and 3.1 (95% CI: 1.19–8.06), respectively. Furthermore, LN patients had significantly higher frequency of D versus I allele compared with lupus patients without nephritis ($\chi^2 = 6.34$ and $p = 0.012$) and controls ($\chi^2 = 8.74$ and $p = 0.013$). The OR for the risk of nephropathy in LN patients with D versus I allele compared with lupus patients without nephritis and controls was 3.47 (95% CI: 1.28–9.44) and 2.92 (95% CI: 1.23–6.95), respectively.

Table 1 Demographic and clinical features of SLE patients

Feature	*SLE group* (n = *50*)
• Age (years)	
Range	21–43
Mean ± SD	31.3 ± 6.5
• Age at disease onset (years)	18–39
Range	27 ± 6.3
Mean ± SD	
• Disease duration (years)	2–7
Range	4.3 ± 1.4
Mean ± SD	
• Fever	18/50 (36%)
• Body mass index (BMI)	23.517.6
• Hypertension	6/50 (12%)
• Oral ulcers	25/50 (50%)
• Malar rash	22/50 (44%)
• Photosensitivity	21/50 (42%)
• Alopecia	4/50 (8%)
• Lupus headache	8/50 (16%)
• Serositis	18/50 (36%)
• Arthritis–arthralgias	24 (48%)–20/50 (40%)
• Renal affection	35/50 (70%)
• Hematological abnormalities	42/50 (84%)
• Vasculopathy	17/50 (34%)
• Neuropsychiatric disorders	5/50 (10%)
• Seropositive ANA	44/50 (88%)
Homogenous pattern	
Speckled and rim patterns	
• Seropositive Anti- DNA	36/44
• SLEDAI score	5/44 - 3/44
Range	36/50 (72%)
Mean ± SD	4–30
	14.34 ± 5.32

Association between ACE enzyme level and I/D gene polymorphism with clinical and laboratory parameters

There was no association between ACE enzyme levels and ACE genotypes with malar rash, discoid rash, photosensitivity, arthritis, serositis or body mass index (BMI). Regarding the laboratory

Table 2 Distribution of ACE genotypes, alleles and mean serum ACE levels in SLE group compared with controls

	SLE group (n = *50*)	*Control group* (n = *29*)	P *value*
ACE genotype, *n* (%)[a]			
DD	31 (62%)	10 (34.5%)	
DI	17(34%)	19 (65.5%)	*0.02*
II	2 (4%)	0 (0 %)	
Allele frequency[b]			
D	79 (79%)	39 (67.2%)	0.1
I	21 (21%)	19 (32.8%)	
Mean serum ACE level (U/L)	40.03 ± 14.91	30.56 ± 12.44	*0.006*

[a] $\chi^2 = 7.84$, $p = 0.02$ for ACE genotypes in SLE patients versus controls, in a 3×2 contingency table.
[b] $\chi^2 = 2.68$, $p = 0.1$ for allele frequency in SLE patients versus controls, in a 2×2 contingency table.

Table 3 Distribution of ACE genotypes, alleles and mean serum ACE levels in LN, lupus patients without nephritis and control groups

	LN patients (n = *35*)	*Lupus patients without nephritis* (n = *15*)	*Controls* (n = *29*)	p *value*
ACE genotype, *n* (%)[a]				
DD	25 (71.4%)	6 (40%)	10 (34.5%)	
DI	10 (28.6%)	7 (46.7%)	19 (65.5%)	*0.002*
II	0 (0%)	2 (13.3%)	0 (0%)	
Allele frequency[b]				
D	60 (85.7%)	19 (63.3%)	39 (67.2%)	
I	10 (14.3%)	11 (36.7%)	19 (32.8%)	*0.016*
Mean serum ACE level (U/L)[c]	40.55 ± 15.42	38.99 ± 14.8	30.56 ± 12.44	*0.02*

[a] Fisher's exact test (p-value) = 0.002 for ACE genotypes in LN, lupus patients without nephritis and controls, in a 3×3 contingency table.
[b] $\chi^2 = 8.25$, $p = 0.016$ for allele frequency in LN, lupus patients without nephritis and controls, in a 2×3 contingency table.
[c] The mean serum ACE level was significantly higher in the LN group compared with controls ($p = 0.008$).

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parameters there was no correlation with hematological abnormalities, but on the other hand, mean 24-h proteinuria was significantly higher in LN patients with DD compared with those with DI genotype (3.51 ± 0.85 *vs.* 2.38 ± 1.17 g, $p = 0.003$). Statistically significant positive correlations were found between serum ACE level and serum creatinine and C3 levels ($r = 0.39$, 0.42 and $p = 0.03$, 0.02, respectively). Furthermore, serum ACE level showed significant positive correlation with 24-h proteinuria ($r = 0.47$ and $p = 0.009$).

Relation of histopathological findings of lupus nephropathy with ACE enzyme level and ACE genotypes

As represented in Table 4, according to WHO classification, five (14.3%) LN patients had class II, 12 (34.3%) had class III and 18 (51.4%) had class IV glomerulonephritis. No significant difference was found in ACE genotype between classes II, III and IV (Fisher's exact test, $p = 0.59$). The frequency of ACE DD versus DI genotype was significantly higher in SLE patients with class III (Fisher's exact test, $p = 0.005$) and class IV (Fisher's exact test, $p = 0.03$) glomerulonephritis compared with controls. No significant difference was found in mean serum ACE levels between classes II, III and IV ($p = 0.87$).

ACE enzyme level and I/D gene polymorphism in SLE patients with vasculopathy

Seventeen SLE patients had vascular manifestations including Raynaud's phenomenon and/or cutaneous vasculitis. As shown in Table 5, SLE patients with vasculopathy had significantly higher frequency of DD versus DI/II genotypes compared with SLE patients without vasculopathy (Fisher's exact test, $p = 0.04$) and controls ($\chi^2 = 9.84$ and $p = 0.002$). The OR for the risk of vascular morbidity in SLE patients with vasculopathy having ACE DD versus (DI/II) compared with SLE patients without vasculopathy and controls was 4.39 (95% CI: 1.1–18.2) and 8.87 (95%CI: 2.05–38.3), respectively. In addition, SLE patients with vasculopathy had significantly higher frequency of D versus I allele compared with SLE patients without vasculopathy ($\chi^2 = 4.6$ and $p = 0.03$) and controls ($\chi^2 = 6.75$ and $p = 0.009$). The OR for the risk of vascular morbidity in SLE patients with vasculopathy having D versus I allele compared with SLE patients without vasculopathy and controls was 3.88 (95% CI: 1.1–14.26) and 5.03 (95% CI: 1.36–18.58), respectively.

SLE patients with and without vasculopathy and controls showed significant difference in mean serum ACE levels ($p = 0.009$). It was significantly higher in SLE patients with vasculopathy than in controls (42.67 ± 9.67 *vs.* 30.56 ± 12.44 U/L, $p = 0.001$).

Association between ACE enzyme level and I/D gene polymorphism and SLEDAI scores

SLE patients with DD genotype had statistically significant higher mean SLEDAI scores than those with (DI/II) genotypes (15.68 ± 5.39 *vs.* 12.16 ± 4.52, $p = 0.02$). Furthermore, a significant positive correlation was found between serum ACE levels and SLEDAI scores ($r = 0.32$ and $p = 0.04$).

Table 4 Distribution of ACE genotypes and mean serum ACE in class II, III and IV glomerulonephritis for 35 patients with lupus nephritis

	Class II (n = *5*)	*Class III* (n = *12*)	*Class IV* (n = *18*)
ACE genotype, *n* (%)[a]			
DD	3 (60%)	10 (83.3%)	12 (66.7%)
DI	2 (40%)	2 (16.7%)	6 (33.3%)
Mean serum ACE level (U/L)	38.4 ± 24.2	42.5 ± 13.02	39.8 ± 15.85

[a]Fisher's exact test (p-value) = 0.59 for ACE genotypes in classes II, III and IV glomerulonephritis, in a 2×3 contingency table.

Table 5 Distribution of ACE genotypes, alleles and mean serum ACE levels in SLE patients with and without vasculopathy and control groups

	SLE patients with vasculopathy (n = *17*)	*SLE patients without vasculopathy* (n = *33*)	*Control group* (n = *29*)	p *value*
ACE genotype, *n* (%)[a]				
DD	14 (82.35%)	17 (51.5%)	10 (34.5%)	
DI	3 (17.65%)	14 (42.4%)	19 (65.5%)	*0.007*
II	0 (0%)	2 (6.1%)	0 (0%)	
Allele frequency[b]				
D	31 (91.2%)	48 (72.7%)	39 (67.2%)	
I	3 (8.8%)	18 (27.3%)	19 (32.8%)	*0.04*
Mean serum ACE level (U/L)	42.67 ± 9.67	39.15 ± 16.4	30.56 ± 12.44	*0.009*

[a]Fisher's exact test (p-value) = 0.007 for ACE genotypes in SLE patients with and without vasculopathy and control groups, in a 3×3 contingency table.

[b]$\chi^2 = 6.72$, $p = 0.04$ for allele frequency in SLE patients with and without vasculopathy and control groups, in a 2×3 contingency table.

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Discussion

SLE is a disorder of generalized autoimmunity with unknown etiology that is known to occur in genetically susceptible patients influenced by environmental factors.[16] It is possible that 40 or more different genes may confer lupus susceptibility and that these susceptibility genes may differ between populations.[1] To our knowledge, this study is the first report showing an association of ACE genotyping and ACE serum levels with SLE in an Egyptian population.

Based on the biological function and chromosomal location, ACE has been considered one of the possible candidate genes in SLE, where vasculitis and vascular changes are frequently found.[11,17]

Since immunological abnormalities appear to be directly related to the disease process of SLE, it is reasonable to predict that ACE gene polymorphisms may contribute to SLE susceptibility by affecting the function of the ACE protein or the systemic or local concentrations of ACE, which subsequently alters the immunological response in patients with lupus.[18]

The ACE I/D polymorphism is located in an intron of the ACE gene, and this polymorphism is in strong linkage disequilibrium with genetic factors that influence serum ACE concentration, and it accounts for about one-half of the variance in ACE plasma levels in humans.[11] In this study, subjects with DD genotype had a significantly higher mean level than those with DI (39.73 ± 13.15 *vs.* 32.02 ± 14.04 U/L, $p = 0.015$) and II genotypes (39.73 ± 13.15 *vs.* 16.95 ± 1.06 U/L, $p = 0.02$).

There is some evidence for increased RAS activation in autoimmune diseases. As early as 1987, ACE activity was found to be increased in the serum of patients with SLE and RA.[19] In accordance, SLE patients in the current work (and LN group) had significantly higher mean serum ACE levels compared with controls.

Studies on ACE I/D polymorphism in SLE have shown controversial results. This discrepancy is not surprising; there are several possible explanations such as clinical heterogeneity, ethnic difference or real genetic heterogeneity, small sample size and inadequate statistical power, but the exact reasons remains unclear.[17]

In the literature, some studies have shown increased DD genotype and D allele frequencies in SLE compared with a control group,[20,21] and susceptibility to SLE.[22] Similarly, our SLE patients showed significantly higher DD genotype and D allele frequencies and, compared with controls, DD genotype was associated with increased risk of developing SLE. On the contrary, others have shown increased frequency of DD genotype in controls when compared with lupus patients[23] or no difference in ACE genotype distribution between both groups.[8,17,24,25]

DD genotype was shown to be significantly higher in LN patients than in normal controls, which coincides with the studies done among Brazilian[26] and Pakistani populations.[27] However, the DD genotype was not associated with the clinical and pathological characteristics of LN and ID genotype was associated with severity and poor prognosis.[28] SLE patients with II genotype had lower proteinuria and creatinine levels than those with DD genotype.[21]

In the present study, DD genotype and D allele were significantly more frequent in the LN group and associated with increased risk of nephropathy compared with both lupus group and controls. Moreover, DD genotype and increased serum ACE levels were associated with higher levels of 24-h proteinuria and serum creatinine. No association was found between ACE genotype distribution and serum ACE levels and severity of pathologic renal lesion.

On the other hand, a study of 84 Japanese SLE cases has found an association between II genotype and increased activity of LN[29] or no differences between ACE genotype distribution and lupus nephritis and its related parameters as seen amongst Koreans,[8] African-Americans,[23] Israelis[24] and Kuwaiti SLE patients.[25]

The role of ACE polymorphism remains unclear in the pathogenesis of SLE and LN.[17] Factors that discriminate the individual susceptibility to the development and progression of renal disease in SLE are not completely identified. Differences in individuals' response to RAS blockade may be in part genetically determined, with the participation of genetic polymorphism of this system.[6]

Vasculopathy is a common manifestation in SLE, either in the form of mucocutaneous vasculitis, a vasculitis associated with visceral organ impairment, thrombotic event, or Raynaud's phenomenon. However, the precise genetic factor associated with vasculopathy has not yet been identified.[8] The DD genotype was associated with endothelial dysfunction, which is a prominent finding in Raynaud's phenomenon, due to blunting of stimulated endothelial or donated nitric oxide response, suggesting that the prevalence of Raynaud's phenomenon might be higher in patients with DD genotype.[8,30]

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A significant association of the DD genotype with Raynaud's phenomenon in lupus patients was reported for the first time in 2007 and DD genotype presence may confer susceptibility to the development of vascular morbidity.[25] In agreement, our data showed that DD genotype and D allele were significantly more frequent in SLE patients with vasculopathy. Emphasizing our data was the study done by Al-Awadhi et al. in a Kuwaiti population.[25] In addition, mean serum ACE level was significantly higher in SLE patients with vasculopathy than in controls.

Earlier studies had demonstrated negative association of the DD genotype with Raynaud's phenomenon and other vascular morbidities.[8,24] The presence of additional factors other than ACE polymorphism which could affect the presence of Raynaud's phenomenon or immunoreactive ACE level[11] can explain this discrepancy of results.

In the present study, SLE patients with DD genotype had a significantly higher mean SLEDAI score and serum ACE. In contrast, Sato and co-workers revealed that patients with II or ID genotype had significantly higher SLEDAI score,[31] and Molad and associates failed to find any significant association between the ACE genotype and SLEDAI.[24] Racial and genetic differences can be possible reasons for this discordance of data.

A limitation of our study was the small number of patients. Further evaluation is needed in a large cohort of patients to determine the exact prevalence of ACE gene polymorphism amongst Egyptian SLE patients.

In conclusion, the associations observed in the current work highlight the potentially important role of ACE genotype and subsequently serum ACE level in the pathophysiology and disease activity of Egyptian SLE patients. Furthermore, ACE deletion polymorphism might be used as a predictive factor for the activity of SLE.

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Conflict of interest statement

The authors have no conflicts of interest.

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