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Angiotensin-Converting Enzyme (*ACE*) D Allele as a Risk Factor for Increase Serum Interleukin-6 and Interleukin-8 in Psoriasis Patients

Ahmed I. Abd Elneam[1,2*], Mohammed Saleh Al-Dhubaibi[3], Ali Ismaiel Ali Abd Alrheam[4]

[1]Molecular Genetics and Enzymology Department, Human Genetics Division, National Research Centre, 33 El Bohouth St. (former El Tahrir St.), Dokki 12622, Cairo, Egypt; [2]Department of Clinical Biochemistry, Faculty of Medicine Al-dawdmi, Shaqra University, Saudi Arabia; [3]Department of Dermatology, Faculty of Medicine Addawdmi, Shaqra University, Saudi Arabia; [4]Department of Clinical Laboratory, Faculty of Applied Medical Science Al-dawdmi, Shaqra University, Saudi Arabia

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***Correspondence:** Ahmed I Abd Elneam. Molecular Genetics and Enzymology Dept., Human Genetics Division, National Research Centre, 33 El Bohouth St. (former El Tahrir St.), Dokki 12622, Cairo, Egypt; Department of Clinical Biochemistry, Faculty of Medicine Al-dawdmi, Shaqra University, Saudi Arabia. E-mail: drahmedabdelneam@gmail.com

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Abstract

BACKGROUND: Psoriasis is a chronic, recurrent inflammatory skin disease. It is characterised by autoimmune, environmental factors and complex genetic disorder.

AIM: To explore the role of IL-6, IL-8, and *ACE* I/D polymorphism in the pathogenesis of Psoriasis and investigation of the relationship between *ACE* polymorphism and occurrence of psoriasis.

PATIENTS AND METHODS: In this study, we took 73 psoriasis patients and 47 healthy patients as a control. These two groups subjected to analysis for *ACE* gene I/D polymorphism by PCR and biochemical methods.

RESULTS: The serum levels of ACE, IL-8 and IL-6 were statistically significantly higher in psoriasis patients compared to healthy subjects ($P < 0.001$). ID and DD polymorphism were more common in psoriasis patients than healthy subjects. Also, D allele was significantly over-represented in patients compared to controls (52.7% Vs 35.1%).

CONCLUSION: *ACE* gene polymorphism might grant susceptibility to develop psoriasis.

Introduction

Psoriasis is a chronic, recurrent inflammatory skin disease that can have a great effect on a patient's self-esteem [1]. It is affected by autoimmune, environmental factors and complex genetic disorder [2]. The effect of the disease is not only limited solely to the skin but also causes permanent joint damage in nearly 30% of the patients [3].

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase, located on chromosome 17q23. It contains an insertion (I)/deletion (D) polymorphism within intron 16 that contain the most genetic variables of the variability of serum ACE activity and is associated with the development of psoriasis [4].

Several studies indicated that Angiotensin-converting enzyme is a major and effective factor in creating angiotensin II (Ang II) and inactivating bradykinin [5] [6].

Active angiotensin II increases the production of reactive oxygen species (ROS) and the synthesis of cytokines such as interleukin-6 (IL-6) and IL-8 which play an important role in the development of psoriasis [7]. Also, inactivation of bradykinin by ACE stimulates the synthesis of cytokines such as IL-6, IL-8 and nitric oxide (NO) [8] [9] [10].

Interleukin 6 (IL-6) is a major inducer of regulated expression of many cytokines [11]. IL-6 is one of the normal skin components, and it was immunologically founded in endothelial cells, keratinocytes, and fibroblasts [11]. IL-6 has been suggested to function as an autocrine mitogen in the psoriatic epidermis [12].

Interleukin 8 (IL-8) is one of the most common chemokines that is elevated in the psoriatic lesion [13]. Moreover, both mRNA and peptide IL-8 have been detected in situ in psoriatic patients [14]. Elevated IL-8 blood levels are considered as a marker for the systemic inflammatory disorders [15].

Our main goal was to explore the role of IL-6, IL-8, and *ACE* I/D polymorphism in the pathogenesis of Psoriasis. Also, our specific aim is to investigate the relationship between *ACE* polymorphism and occurrence of psoriasis.

Subject and Methods

The present study was performed at Outpatient Dermatology Clinic, Buraidah Central Hospital, Qassim region, Saudi Arabia between October 2016 and May 2017.

A total of 73 patients (42 male and 31 females) were enrolled for this case-control study. The diagnosis was established by clinically-physical examination as the diagnosis was striated forward (All patients had characteristic erythematosquamous plaques located on the trunk and limbs). Patients had an only cutaneous form of psoriasis, with no systemic involvements were included in the study. None of the patients had received any systemic immunosuppressive medications or used any local treatment at the site of biopsies for 4 weeks before study participation.

Patients were classified according to body surface area (BSA) into severe psoriasis vulgaris greater than 10% of the body surface, moderate psoriasis vulgaris 5%-10% of the body surface and mild psoriasis vulgaris less than 5% of the body surface [16].

The other 47 subjects were healthy volunteers who were age and gender-matched with the psoriasis group (27 male and 20 females), they had no clinical evidence or family history of psoriasis or any other autoimmune disorder.

Both groups had undergone complete physical and clinical examinations, genetics studies and biochemical tests.

Before the initiation of the study, informed consent was obtained from all individuals chosen for the study. The aim and the value of the work were explained to them in a simplified manner. This study was approved by the Local Medical Ethical Committee and according to their instructions.

Serum ACE concentrations were measured, utilising the Human ACE Quantikine ELISA Kit from R&D Biotech brand system [17].

The interleukin-6 level was determined using a commercially available ELISA kit (Quantikine, human IL-6R & D Systems, Minneapolis, USA) by the manufacturer's instructions [18].

Serum IL-8 samples from all patients were tested in a sandwich ELISA using according to the manufacturers' instructions (R&D, Minneapolis, USA; Bender, Vienna; Amersham, Germany) [19].

Blood samples were collected on Na_2EDTA as an anticoagulant. Genomic DNA was purified from 200 µl whole blood with the QIAamp® DNA BloodMini Kit according to manufacture instruction for Blood protocol.

To determine the *ACE* gene I/D polymorphism, a genomic DNA fragment on intron 16 of the *ACE* gene was amplified by using Polymerase Chain Reaction (PCR) method with a pair of oligonucleotide primers: The upstream of primer sequence was: 5`-CTG GAG ACC ACT CCC ATC CTT TCT -3` and the downstream was: 5`- GAT GTG GCC ATC ACA TTC GTC AGA T -3` (20). The primers were blasted to the gene bank database https://blast.ncbi.nlm.nih.gov/Blast.cgi [21].

Data was presented by means ± SD and percentages. The compiled data were computerised and analysed by SPSS PC+, version 12. The following tests of significance were used: Analysis of variance (ANOVA) test between more than two means, t-test between means we used to analyse the mean difference, t-test between percentage to analyse percent difference and chi-square. A level of significance with $p \leq 0.001$ was considered highly significant and $p > 0.05$ was considered insignificant.

Results

In our present study, we analysed *ACE* gene polymorphism for Seventy–three (42 male and 31 females) psoriasis patients and Forty –seven (27 male and 20 females) healthy controls they had no clinical evidence or family history of psoriasis or of any other autoimmune disorder. Clinical and General Data of all the patients and controls are shown in Table 1. It was noted that serum ACE, serum IL-8 and serum IL-6 were statistically significantly higher in psoriasis patients than in healthy subjects ($P < 0.001$).

Clinical presentation of psoriasis showed that 23 patients (31.5%) have severe psoriasis vulgaris, 26

patients (33.5%) have moderate psoriasis vulgaris and 24 patients (33%) have mild psoriasis.

Table 1: General and laboratory characteristics of psoriatic patients and healthy control

Parameters	Patients N (73) Mean ± SD	Control N (47) Mean ± SD	P-value
Age/years (Mean ± SD)	41.2 ± 4.8	38.1 ± 6.8	0.411
Male/Female (N, %)	42(57.5%)/31(42.5%)	27(57.4%)/20(42.6%)	0.442
Severe psoriasis vulgaris (N, %)	23 (31.5%)		
Moderate psoriasis vulgaris (N, %)	26 (33.5%)		
Mild psoriasis vulgaris (N, %)	24 (33%)		
Presence of Family history (N, %)	46/63%		
Absent of Family history (N, %)	27/37%		
Serum ACE (IU/L)	21.7 ± 5.5	7.7 ± 4.1	<0.001*
Serum IL-6 (pg/ml)	17.5 ± 0.48	8.9 ± 0.60	<0.001*
Serum IL-8 (pg/ml)	15.9 ± 0.9	7.6 ± 1.5	<0.001*

SD, standard deviation; ACE, angiotensin-converting enzyme; IL-6, interleukin-6; IL-8, interleukin-8; N, Number; *Significance between healthy Subjects and psoriatic patients (P<0.05).

Comparison of ACE genotypes in patients and controls showed that I/D were the most common (45.2%) followed by D/D (30.1%) then I/I (24.7%). I/I was the most common in healthy subjects (46.8%) while I/D and D/D genotypes were found to be 36.2% and 17% respectively (Table 2).

Table 2: Comparison of ACE genotype in psoriatic patients and healthy control

Genotypes	Patients (N,%)	Control (N,%)	P-Value
I/ I	18 (24.7 %)	22 (46.8%)	0.007*
I/D	33 (45.2 %)	17 (36.2%)	0.872
D/D	22 (30.1 %)	8 (17 %)	0.001*

N, number; *p value<0.05 is statistically significant.

The allele frequency was significantly different between patients and controls (P = 0.005). The results indicated that the D allele was significantly over-represented in patients compared to the controls (52.7% vs 35.1 %) (Table 3).

Table 3: Comparison of allele frequency in psoriatic patients and healthy control

Alleles frequency	Patients (N, %)	Control (N, %)	P-Value
I	69 (47. 3%)	61 (64.9 %)	0.005
D	77 (52.7 %)	33 (35.1%)	0.002

N, number; *p value<0.05 is statistically significant.

Patients with DD genotypes have statistically significantly higher levels of serum ACE (P < 0.001), higher serum IL-8 (P < 0.001) and higher serum IL-6 (P < 0.001), Table 4.

Table 4: Comparison of biochemical parameters and *ACE* genotypes in psoriatic patients

Parameters	I/ I (n = 18)	I/D (n = 33)	D/D (n = 22)	P-value
Serum ACE (IU/L)	16.88 ± 4.22	23.66 ± 1.66	28.07 ± 3.21	0.001*
Serum IL-6 (pg/ml)	23.67 ± 2.9	39.24 ± 1.54	47.22 ± 2.5	0.001*
Serum IL-8 (pg/ml)	12.66 ± 2.3	18.34 ± 1.6	28.32 ± 4.1	0.001*

SD, standard deviation; ACE, angiotensin-converting enzyme; IL-6, interleukin-6; IL-8 interleukin - 8; N, Number; * Significance between healthy Subjects and psoriatic patients (P < 0.05).

Comparison of biochemical parameters and variable clinical types of psoriasis indicated that the levels of serum ACE, serum IL-6, and IL-8 higher in Severe psoriasis vulgaris patients than in those with Moderate psoriasis and Mild psoriasis vulgaris with P-values 0.012, 0.001 and 0.008 respectively (Table 5).

Table 5: Comparison of biochemical parameters and variable clinical types of psoriasis in our patients

Parameters	Severe psoriasis vulgaris (N = 23)	Moderate psoriasis vulgaris (N = 26)	Mild psoriasis vulgaris (N = 24)	P-value
Serum ACE (IU/L)	23.25 ± 1.21	18.9 ± 2.88	14.79 ± 2.7	0.012*
Serum IL-6 (pg/ml)	38.5 ± 4.5	21.56 ± 3.9	17.44 ± 2.55	0.001*
Serum IL-8 (pg/ml)	22.3 ± 3.8	14.99 ± 2.88	11.23 ± 1.3	0.008*

SD, standard deviation; ACE, angiotensin-converting enzyme; IL-6, interleukin-6; IL-8 interleukin -8; N, Number; * Significance between healthy Subjects and psoriatic patients (P < 0.05).

Our results showed that D/D genotype was more common with severe psoriasis vulgaris (52.2%). On the other side, I/D was more frequent in Moderate psoriasis vulgaris and Mild psoriasis vulgaris patients (50% and 58.3% respectively) (Table 6).

Table 6: Comparison of ACE genotypes and variable clinical types of psoriasis in our patients

Parameters	I/I (N, %)	I/D (N, %)	D/D (N, %)	P-value
Severe psoriasis vulgaris (N = 23)	5 (21.7%)	6 (26.1 %)	12 (52.2 %)	0.001*
Moderate psoriasis vulgaris (N = 26)	6 (23.1%)	13 (50%)	7 (26.9%)	0.001*
Mild psoriasis vulgaris (N = 24)	7(29.1%)	14 (58.3%)	3 (12.6%)	0.001*

*Significance between healthy Subjects and psoriatic patients (P < 0.05).

Discussion

The present study provides a relationship between ACE I/D polymorphism, IL-6, IL-8 and psoriasis as a risk factor was determined.

Our results indicated that psoriasis patients have serum IL-6 and serums IL-8 were significantly higher than in controls (P < 0.001). Our results are in line with several studies [22] [23] [24] they reported that elevated levels of serum IL-6 and serum IL-8 in psoriasis vulgaris patients.

The results of the current study indicated that the ACE polymorphism of the I/I genotype was more frequent in controls (46.8%) than in psoriasis patients (24.7%), while the I/D and the D/D genotypes were more abundant in psoriasis vulgaris patients (45.2% and 30.1% respectively). However, this difference was statistically not highly significant, and this can be explained by the small sample size of our study. Also, we observed that DD genotype was more common in patients with severe psoriasis vulgaris (52.2%) than those with intermediate (26.9%) and mild (12.6%) disease. These results are consistent with Song et al., 2015 who revealed that frequency of DD and ID in case more than II [25].

Our results revealed that D allele was significantly higher in the psoriasis patients (52.7%) than in controls (35.1%). These results were consistent with Min Huang et al., 2017. Who found that the D allele was frequency higher in psoriasis patients than in the controls (43.8% and 31.8% respectively) [26].

Multiple studies have been performed to detect the polymorphisms as an important factor in the development of psoriasis: *TNF α* gene -238G/A

polymorphism [27] -2518 A/G *MCP-1* and -403 G/A *RANTES* promoter gene polymorphisms [28], *CARD14 rs11652075* polymorphism [29] and support the genetic hypothesis in psoriasis.

Our findings showed that a significant relationship between the serum ACE levels in patients and healthy subjects (P < 0.001). Moreover, we showed a significant difference of the serum ACE levels with the different *ACE* genotypes; psoriasis patients with *ACE* DD genotype showed the highest mean ACE serum level (28.07 ± 3.21), while patients with *ACE* II genotype had the lowest mean serum ACE level (16.88 ± 4.22). In the present study, we observed that DD was associated with increased levels of IL-6 and IL-8 (47.22 ± 2.5 and 28.32 ± 4.1 respectively). Also, comparison of biochemical parameters and variable clinical types of psoriasis in our patients showed increased levels of all variables in patients with severe psoriasis vulgaris compared to those with Moderate psoriasis vulgaris and mild psoriasis vulgaris.

Increased levels of serum ACE, IL-6 and IL-8 in psoriasis patients were due to the important role of ACE in inflammation. Where ACE converts Ang I into Ang II and inactivates bradykinin [30]. Ang II activates cytokines like IL-6 and IL-8, thus exerting proinflammatory effects [6]. This indicates an important role of ACE in the pathogenesis of psoriasis [31].

In conclusion, *ACE* gene polymorphism might confer susceptibility to the development psoriasis.

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