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ORIGINAL CONTRIBUTION

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Tumor necrosis factor α-308 G/A and interleukin 1 β-511 C/T gene polymorphisms in patients with scarring acne

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Summary

Background: Acne is a chronic inflammatory skin disorder which may heal with scarring. Tumor necrosis factor alpha (TNF α) and interleukin 1 β (IL-1β) are considered as the main responsible proinflammatory mediators of acne pathogenesis. Oversecretion of these cytokines was found to be associated with TNF α-308 G>A and IL-1β-511 C<T polymorphisms.

Aim: To evaluate the association of TNF α-308 and IL-1β-511 gene polymorphisms with acne and postacne scarring susceptibility and acne severity.

Methods: Study subjects included 90 patients with acne vulgaris (31 males, 59 females; mean age: 19.6 ± 3.7 years) and 30 healthy controls (11 males, 19 females; mean age: 19.2 ± 5.1 years). Patients were sub-grouped on the basis of acne severity into mild, moderate, and severe acne groups and on the presence postacne scarring into scarring acne and nonscarring acne groups. Peripheral venous blood samples were obtained for performing real-time PCR analysis for detecting TNF α-308 and IL-1β-511 genotypic variants.

Results: Among patients, 21.7% (n = 26) had mild, 22.5% (n = 27) had moderate, 30.8% (n = 37) had severe, and 30% (n = 36) had scarring acne. Genotypic variants of TNF α-308 and IL-1β-511 did not statistically differ between acne patients and controls (*P* values: .245 and .466). When compared in terms of acne severity and the presence of postacne scarring, no statistical significance was observed regarding frequencies of genotypic variants related to the both TNF α-308 and IL-1β polymorphisms ($P > .05$).

Conclusion: TNF α-308 and IL-1β polymorphic variants are not associated with acne and postacne scarring susceptibility and acne severity.

KEYWORDS
acne, IL-1β, polymorphism, scarring, TNF α

1 | INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder of pilosebaceous unit, affecting mainly adolescence ages and young adults.[1] Acne severity may vary from mild acne to severe and nodulocystic form accompanying hypertrophic and atrophic scars.[2] Inflammation is one of the key mechanisms involving acne pathogenesis; however, the etiopathogenesis beneath the development of severe and scarring acne still remains unclear.[3]

Proinflammatory cytokines, especially tumor necrosis factor alpha (TNF α) and interleukin 1 alpha (IL-1α) trigger inflammation in acne formation, especially mediated through the stimulation by Propionibacterium acnes (P. acnes). Comedogenesis is mostly related to IL1 α,[4] and inflammatory cascades are mainly associated with TNF α.[5,6]

Recently, P. acnes is considered to involve in the pathogenesis of acne by activating the inflammasomes and by inducing IL-1β oversecretion in in vivo and in vitro studies.[7,8]

Genetic factors are considered to be important in acne pathogenesis as family history of severe acne is detected in some patients with severe acne.[9] Polymorphisms of genes encoding important cytokines playing key roles in acne pathogenesis attract attention of researchers. Transition of guanin to adenin in the promoter -308 locus of TNF α results in 6- to 9-fold increase in the transcription of the cytokine.[10] The polymorphic variants of TNF α-308 are suggested to be associated with acne formation in different populations.[11-17] The increase in C allele amount (C<T) in the -511 locus of IL-1β leads oversecretion of IL-1β cytokine.[18] When searched, we could not find any report about the association of IL-1β polymorphisms with acne. Therefore, in this study, we hypothesized that genotypic variant involving -308 locus of TNF α gene and -511 locus of IL-1β may be associated with acne, acne severity, and scarring acne.

2 | METHODS

2.1 | Subjects

The prospective case–control study was conducted in the dermatovenereology out-patient clinic between February 2017 and June 2017. Ninety acne patients (31 males, 59 females) and 30 healthy individuals (11 males, 19 females) were enrolled. Individuals who had any systemic disease, hormonal abnormalities, menstrual irregularity, malignancy, HIV/AIDS and who were pregnant, breastfeeding, obese, smoking were not included in the study. Participants were not on any systemic and hormonal therapy and were not on any topical or systemic acne treatment for at least 1 month. Demographic (age, gender, onset age of acne, duration of acne, family history of severe acne, etc.) and clinical features (acne severity score, previous acne treatments, the presence of scarring, scarring type, etc.) were noted in evaluation sheets of each patient. The clinical severity of acne was assessed using Global Acne Grading System (GAGS).[2] According to this scarring system, the six regions (forehead, right cheek, left cheek, nose, chin, upper chest, and back) were graded for acne lesions (≥one comedon = 1; ≥one papule = 2; ≥one pustule = 3; ≥one nodule = 4). The most heavily weighted lesion within each region was noted as acne lesion grade. Local score was the product of acne lesion grade x factor (2 for forehead, right cheek, and left cheek, 1 for nose and chin, 3 for chest and upper back). Global acne score was the sum of all local scores. A score of 1-18 was considered mild; 19-30, moderate; 31-38, severe; and >39, very severe acne severe acne (score: 31-38) according to GAGS. The patients were also divided as patients having scaring acne (SA) and nonscarring acne (NSA). Scarring type (atrophic, hipertrophic)[19] and scarring severity (macular, mild, moderate, or severe) according to the qualitative global acne scarring system[20] were also noted. The study was approved by the local ethics committee. All participants signed informed consent form.

2.2 | Blood sampling and analysis of genetic polymorphisms

Peripheral venous blood samples were obtained from all participants, and DNA was extracted using Qiagen Easy One. All samples were stored at −20°C until all were prepared for analyses. Genetic variants of TNFα-308 G/A and IL-1β -511 C/T polymorphisms were detected using the real-time PCR method with Rotor Gene (Qiagen). Oligonucleotide primers and probes were designed by Real-time PCR (Corbett Research®) software program was used for the analyses.

2.3 | Statistical analyses

SPSS version 15.0 (SPSS Inc., Chicago, Illinois) software program was used for all statistical analyses. Numerical values were expressed as mean ± standard deviation or median; categorical values were expressed as number and percentages. Groups and subgroup analyses were performed by *t* test, Mann-Whitney *U* test, Kruskal-Wallis test, chi-square test, or Fisher's exact test. A *P* value <.05 was considered as statistically significant.

3 | RESULTS

According to GAGS, patients were subclassified into mild, moderate, and severe acne patients. The subgroups and controls were similar related to age, gender; and all acne severity subgroups were similar related to age, gender, acne duration, and onset age of acne (all $P > .05$) (Table 1).

Upon dermatological examination, scarring acne was detected in 36 patients (30%). Scarring acne group (SA) and NSA group were similar related to age, gender, acne duration, and onset age of acne (all $P > .05$) (Table 2).

Genotyping of IL-1β-511 and TNF α-308 locuses was performed for all patients and control subjects. Genotype frequencies for all participants are shown in Tables 3 and 4. The distribution of the GG, GA, and AA genotypes of TNF α-308 and the CC, CT, and TT genotypes of IL-1β-511 was similar between the patients with acne and healthy subjects. These genotypic variants were not found to be associated with acne severity and scarring acne (all $P > .05$).

As the presence of C allele and A allele is associated with increased expression of IL-1β-511 and TNF α-308, respectively, we re-grouped the related genotypes and compared with acne patients and healthy subjects. CC+CT versus TT and GA+AA versus AA groups were similar between patients and controls, and no protective effect of TT and GG genotypes was shown related to acne, acne severity, and scarring acne (Tables 3 and 4).

4 | DISCUSSION

Investigations about the association of TNF α polymorphisms and acne are limited in number.[11-17] In our study, we did not find an

TABLE 1 Demographic characteristics of patients and controls

	Patients			Controls	*P*
Males, n (%)	31 (34.4)			11 (36.7)	.825
Females, n (%)	59 (65.6)			19 (63.3)	
Age (year)*	19.6 ± 3.7 (12-30)			19.2 ± 5.1 (12-30)	.415
	Mild	**Moderate**	**Severe**		
Males, n (%)	9 (34.6)	11 (40.7)	11 (36.7)	11 (36.7)	.658
Females, n (%)	17 (65.4)	16 (59.3)	26 (70.3)	19 (63.3)	
Total	26 (100)	27 (100)	37 (100)	30 (100)	
Age (year)*	20 ± 4.0 (13-30)	19.0 ± 3.4 (12-25)	19.7 ± 3.7 (12-27)	19.2 ± 5.1 (12-30)	.710
Onset age (year)*	15.5 ± 2.7 (12-23)	14.6 ± 1.9 (10-20)	15.2 ± 3.2 (10-24)	–	.628
Acne duration (year)*	4.5 ± 3.3 (1-16)	4.5 ± 3.4 (1-11)	4.5 ± 4.0 (1-12)	–	.910

*mean ± SD (min-max).

TABLE 2 Demographic characteristics of scarring (SA) and nonscarring (NSA) patients and controls

	SA (n = 36)	NSA (n = 54)	Controls (n = 30)	*P*
Males, n (%)	12 (33.3)	19 (35.2)	11 (36.7)	.960
Females, n (%)	24 (66.7)	35 (64.8)	19 (63.3)	
Age (year)*	19.6 ± 3.8 (12-27)	19.6 ± 3.6 (13-30)	19.2 ± 5.1 (12-30)	.686
Onset age (year)*	15.1 ± 3.1 (10-24)	15.1 ± 2.4 (10-23)	–	.637
Acne duration (year)*	4.5 ± 2.8 (1-12)	4.5 ± 3.3 (1-16)	–	.774

*mean ± SD (min-max).

association of TNF α-308 G>A and IL1 β-511 C<T genetic polymorphisms with acne and acne severity. In another study from Turkey, Baz et al investigated only the TNF α-308 polymorphism in a sample of acne patients living in the Mediterranean coast region having heterogeneous ethnic groups and reported that TNF α-308 GA genotype was significantly more frequent in acne patients. They did not find any association between acne severity and TNF α-308 genotypes. Investigations on Polish,[12] Hungarian and Romanian,[13] and Sicilian[15] populations did not declare any association of TNF α-308 genotypes and acne. On the other hand, female patients in Hungarian and Romanian population[13] and male patients in Sicilian population[15] showed significant difference for polymorphic variants. Investigations from different ethnic regions such as Saudi Arabia[14] and Pakistan[17] and three meta-analyses which also included Chinese and Greek participants suggested that the -308 G/A polymorphism in the TNF α gene involves in acne risk.[16,21,22] Among meta-analyses, Li et al[22] declared that TNF α-308 AA genotype is significantly associated with acne severity and male acne patients. Yang et al[21] suggested TNF α-308 genotype is a risk factor for Caucasian acne patients. Grech et al[16] reported that this polymorphic variant is associated with acne severity. All these data and analyses may support the role of TNF α promoter gene polymorphism in acne; however, we suggest that diverse results from different ethnic populations may not be ignored.

The polymorphism investigations about the interleukin family are about the IL-1α gene till now, as this cytokine is known to play important role in comedogenesis. The polymorphic variants of IL-1α at +4845[4] and −889 [23,24] locuses were found to be associated with acne severity. Interleukin 1β is another important proinflammatory cytokine mainly released from activated T lymphocytes and macrophages.[18] The polymorphic variants of IL-1β-511 were detected in brain abscess, chronic periodontitis, and major recurrent depression.[18,25,26] Recent researches about acne pathogenesis point to the role of IL-1β pathways which are stimulated by P. acnes.[7,8] Interleukin 1β mRNA and activated processed IL-1β were measured to be densely accumulated in inflammatory acne lesions. P. acnes is considered to activate NLRP3 inflammasome and IL-1β processing and secretion.[7,8] These data suggested us to investigate the potential role of IL-1β polymorphic variants in acne. To the best of our knowledge, there is no investigation about this issue. We could not find any association between IL-1β-511 genotypic variants and acne or acne severity.

Scarring acne is the result of the damage in pilosebaceous unit surrounding tissue. Scarring may be a sequel of an acne lesion or may emerge from the initial acne development till regression of acne in mainly severe acne or even in mild acne forms. Both genders may be affected and up to 43%-95% of acne patients may experience atrophic or hypertrophic acne scars.[27,28] Although the triggering and exacerbating factors are not clear, humoral and cellular immune mechanisms related to P. acnes and acne severity are considered to involve a key role in the scarring acne pathogenesis. Holland et al demonstrated that patients with scarring acne have a predominant-specific immune response which is weak at initial but hugely activated in regressing acne lesions. A chronic delayed type hypersensitivity reaction is suggested to be triggered by a persistent antigenic stimulus that cannot be eliminated.[3] In

TABLE 3 Frequencies of IL-1β-511 C/T and TNF α-308 G/A genetic variants in acne patients and controls

		IL-1β-511 C/T				TNF α-308 G/A			
	Total n	CC n (%)	CT n (%)	TT n (%)	*P*	GG n (%)	GA n (%)	AA n (%)	*P*
Subjects									
Patients	90	28 (31.1)	46 (51.1)	16 (17.8)	.466	68 (76.6)	12 (13.3)	10 (11.1)	.245
Controls	30	13 (43.3)	13 (43.3)	4 (13.3)		20 (66.7)	3 (10.0)	7 (23.3)	
Male gender									
Patients	31	6 (19.4)	16 (51.6)	9 (29.0)	.076	24 (77.4)	2 (6.5)	5 (16.1)	.940
Controls	11	6 (54.5)	4 (36.4)	1 (9.1)		8 (72.7)	1 (9.1)	2 (18.2)	
Female gender									
Patients	59	22 (37.3)	30 (50.8)	7 (11.9)	.901	44 (74.6)	10 (16.9)	5 (8.5)	.154
Controls	19	7 (36.8)	9 (47.4)	3 (15.8)		12 (63.2)	2 (10.5)	5 (26.3)	
Acne severity									
Mild	26	8 (30.8)	15 (57.7)	3 (11.5)	.509	19 (73.1)	5 (19.2)	2 (7.7)	.568
Moderate	27	11 (40.7)	10 (37.0)	6 (22.2)		21 (77.8)	2 (7.4)	4 (14.8)	
Severe	37	9 (24.3)	21 (56.8)	7 (18.9)		28 (75.7)	5 (13.5)	4 (10.8)	
Controls	30	13 (43.3)	13 (43.3)	4 (13.3)		20 (66.7)	3 (10.0)	7 (23.3)	
Presence of scar									
NSA	54	18 (33.3)	26 (48.2)	10 (18.5)	.734	41 (75.9)	6 (11.1)	7 (13.0)	.451
SA	36	10 (27.8)	20 (55.6)	6 (16.7)		27 (75.0)	6 (16.7)	3 (8.3)	
Controls	30	13 (43.3)	13 (43.3)	4 (13.3)		20 (66.7)	3 (10.0)	7 (23.3)	

TABLE 4 Comparison of allelic variants of IL-1β-511 C/T and TNF α-308 G/A among acne patients and controls

		IL-1β-511 C/T			TNF α-308 G/A		
	Total n	CC+CT n (%)	TT n (%)	*P*	GG n (%)	GA+AA n (%)	*P*
Subjects							
Patients	90	74 (82.2)	16 (17.8)	.572	68 (75.6)	22 (24.4)	.340
Controls	30	26 (86.7)	4 (13.3)		20 (66.7)	10 (33.3)	
Acne severity							
Mild	26	23 (88.5)	3 (11.5)	.690	19 (73.1)	7 (26.9)	.787
Moderate	27	21 (77.8)	6 (22.2)		21 (77.8)	6 (22.2)	
Severe	37	30 (81.1)	7 (18.9)		28 (75.7)	9 (24.3)	
Controls	30	26 (86.7)	4 (13.3)		20 (66.7)	10 (33.3)	
Presence of scar							
NSA	54	44 (81.5)	10 (18.5)	.830	41 (75.9)	13 (24.1)	.632
SA	36	30 (83.3)	6 (16.7)		27 (75.0)	9 (25.0)	
Controls	30	26 (86.7)	4 (13.3)		20 (66.7)	10 (33.3)	

another study, severity of innate immune response in early inflammation in the epidermis is proposed to have a link with acne scarring.[29] Hypertrophic scars and keloids may emerge in consequence of cutaneous injury as observed in acne. Histopathological examinations of keloid tissues revealed upregulation of many proinflammatory cytokines such as IL-1α, IL-1β, IL-6, and TNF α.[30] Early increase in serum decorin and IL-1β levels was detected to be predictive in the development of postburn hypertrophic scars. IL-1β is suggested to have profibrotic effects, and its interaction with local and systemic factors may lead hypertrophic scarring.[31] The limited knowledge about acne scarring and other scarring forms caused by different factors suggested us to investigate and compare the genotypic variants of IL1 β-511 and TNF α-308 in scarring and nonscarring acne patients. Although we could not detect a relationship, we suggest that new studies with large number of patients in different ethnic populations are needed.

Otherwise, we also suggest that T-cell subsets and regulatory mechanisms of T cells also take attention to be investigated in scarring acne as scarring is suggested to be related to a hypersensitivity reaction.[3]

The present study may be a preliminary assessment of the role of genetic polymorphic variants of two important cytokines, TNF α and IL-1β, in the pathogenesis of scarring acne. As acne is a multifactorial and potentially multigenetically influenced disorder, investigations about other genotypic variants may have key roles in acne pathogenesis of different populations. For instance, polymorphic variants of different locuses of TNF α and IL-1β genes or factors effecting the expression of these genes and secretion of their cytokine products may have important roles in acne and scar formation. Furthermore, other proinflammatory cytokines and defects of anti-inflammatory cytokines and their genotypic variations may be responsible for acne and scarring. More detailed investigations about the common pathways and cytokine profiles of scar formation process and acne are also needed for better understanding of scarring acne pathogenesis.

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CONFLICT OF INTEREST

None.

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