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ORIGINAL ARTICLE

Evaluation of Interleukin *17A* Gene (rs 2275913) polymorphism in Patients with Diabetic Foot Ulcer

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ABSTRACT

Background*: Diabetic foot ulcer (DFU) is one of the most serious complications – occur on the foot of individuals with diabetes, leading to infections, hospitalization and even amputation if not properly managed. Interleukin-17A (IL-17A) is a pro-inflammatory cytokine that plays a crucial role in the development of autoimmune and inflammatory diseases and in the immune responses against infections.* ***Objective:*** *The current study aimed to explore the relation of the IL-17A (rs2275913) G/A gene polymorphism with severity and progression of foot ulcers caused by diabetes.* ***Methodology****: This case-control research included 35 cases of ulcerated diabetic feet and 35 healthy Individuals as a control. DNA extraction was done to reveal the polymorphism of the IL-17A gene by allele-specific polymerase chain reaction.* ***Results****: A statistically significant difference (P = 0.095) was observed between the study groups regarding the genotypes of IL-17A gene polymorphism. The AA and GA genotypes were more prevalent in cases, although the frequency of GG genotypes was higher in controls compared to patients. The frequency of the A allele was elevated in patients compared to controls. Conversely, the allele G was less prevalent in cases compared to the control group, yielding a significant result (P=0.0187).* ***Conclusion****: This study demonstrated that the AA genotype was more prevalent in patients with diabetic foot ulcer compared to the control group. Thus, it is possible that the AA genotype contributes to the risk of diabetic foot ulcer.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic condition marked by elevated blood glucose levels and disrupted metabolism of carbohydrates, fats, and proteins due to a relative or total deficiency of the hormone insulin; one of its effects is diabetic foot syndrome[1].

Diabetic foot syndrome (DFS) is a significant consequence of diabetes mellitus (DM), characterized by infection, ulceration, and/or destruction of deep tissues, coupled with neurological problems and/or variable degrees of limb ischemia[2].

Infection in the deep tissues resulting from ulceration and destruction is associated with neurological abnormalities in various circumstances of diabetic individuals with peripheral arterial disease (PAD) in the lower leg. Under this condition, the skin's protective layer becomes infected due to bacterial contamination, while the epidermis sustains damage. In diabetic individuals with diabetic foot ulcers, amputation is necessary to mitigate infection in the lower extremities[3]**.** Trauma significantly contributes to the development of ulceration[4]. Diabetic individuals may have an increase in diabetic foot ulcers when their work environment facilitates infection. The employment of diabetes patients significantly influences the onset of diabetic foot ulcers (DFU)[3].

The worldwide incidence of diabetic foot varies between 9.1 and 26.1 million, with an overall prevalence of around 6.3%, mostly affecting those with type 2 diabetes, the elderly, and those with prolonged diabetes duration[5]**.**

Approximately 50% to 60% of people with diabetic foot ulcers (DFU) may get diabetic foot infections (DFI), and 15% may need amputation. The five-year mortality risk in persons with diabetic foot ulcers is 2.5 times greater than in those without foot ulcers[6]**.** DFU infection severity was classified into uninfected, mild infection, moderate infection and severe infection[7]**.** Males, type 2 diabetics, older people, hypertension, diabetes duration, reduced body mass index (BMI), diabetic retinopathy (DR), and smoking history were more likely to have diabetic foot ulcers (DFU)[8]**.**

In diabetic wounds, healing is delayed and problems are exacerbated owing to inadequate blood flow, diminished oxygen levels, and elevated glucose concentrations. Tissue necrosis results from diminished circulation, whereas neuropathy causes sensory and motor impairment in the skin of the lower limbs, exacerbated by bacterial infections. Normal wound healing can be delayed due to a decrease in advantageous inflammatory factors and an elevation in detrimental inflammatory factors[6]**.**

The immune system plays a critical role in the development, progression, and healing of diabetic foot ulcers (DFUs). However, in diabetes, immune dysfunction compromises the body's ability to fight infections and heal wounds, making DFUs more severe and harder to treat.

Interleukin 17A (IL-17A) is a member of the IL-17 family, which consist of six cytokines (IL-17A to IL-17F). Members of the IL-17 family are conventionally regarded as powerful proinflammatory cytokines mostly released by Th17 cells, while they are also generated by several other cells, including natural killer (NK) cells, macrophages , neutrophils, dendritic cells, and mast cells[9]**.** IL-17A is an effective pro-inflammatory cytokine that induces early innate immune responses to infections and contributes to autoimmune and inflammatory illnesses. IL-17A has a role in the immunological illnesses including systemic lupus erythematosus, multiple sclerosis, graft rejection, type 1 diabetes, asthma, and nephrotic syndrome[10]**.** IL-17 is essential for host defense against bacterial and fungal pathogens such as *Klebsiella pneumoniae, Listeria monocytogenes,* and *Candida albicans*[11]**.**

The IL-17A signaling pathway activates the genes for proinflammatory cytokines such as IL-1β, TNF-α, and IL-6[12]. A large number of diseases were significantly associated with rs2275913 single nucleotide polymorphism (SNP) in the *IL-17A* gene promoter. The variations in *IL-17A* secretion were associated with bind of allelic variants of rs2275913 (SNP) to the nuclear factor of activated T cells[13]**.** *IL-17* gene is situated on both sides human chromosome 6p12.2. It is similar functions (almost 50%) as that of chromosome 6 and shares 50% amino acid with this chromosome. There was increased production of *IL-17A* in diabetic patients, which was mostly stimulated by monocytes. One study reported that *IL-17A* polymorphism related with diabetes, and also has a role in chronic and aggressive type of periodontal disease[14]**.**

METHODOLOGY

This study was a case- control study. The study was done on 70 participants divided into two groups: The first group is the cases group, which consists of 35 patients with diabetic foot ulcer who attended to Al-lmam Al-Hassan Center for Endocrinology and Diabetes in the holy city of Karbala during the period extended from December (2024) to March (2025) and the patients were previously diagnosed by physicians specialized in endocrinology and diabetes. The second group was the control group, consisting of 35 healthy individuals. Two ml of Venous blood under aseptic Conditions from each participant were dispensed into two EDTA tubes (one 1 ml in each tube) for laboratory and molecular testing and stored at -20 °C for allele specific polymerase chain reaction (PCR) technique for estimation of *IL-17A* gene polymorphism.

Inclusion criteria:

All patients with diabetic foot ulcer were diagnosed on the basis of clinical symptoms and laboratory investigations.

Exclusion criteria: Patients who have wounds other than diabetic foot ulcer, infection anywhere, autoimmune disease or cancer.

PCR of *IL-17A* gene polymorphism:

Blood samples from each participant were collected in EDTA tubes and kept at -20 °C until DNA extraction. According to the procedure of the ADD BIO / Korea Genomic, DNA was extracted from each participant. The constituents of the PCR mixture were allocated into the two PCR tubes provided with the kit. A 25 microliters PCR mixture that included (3 microliters of DNA, 5 microliters of premix, 2 microliters of forward allele A was placed in the first tube and forward allele G in the other tube, 2 microliters of reverse allele common were added to each of them, and 13 microliter of nuclease-free water). The tubes were meticulously mixed using the vortex device for 5 seconds, thereafter transferred to the PCR thermal cycler to undergo heat cycles under optimal conditions for DNA amplification.

The Primers that were used in this study is shown in table 1

Table 1: Primer Sequences Used for IL-17A Gene Polymorphism Detection (rs2275913

Primer Type	Sequence (5' to 3')	Product Size
Allele A specific forward	5'ATGGTGTTTAATCTCATCTGTGGGG3'	312 bp
Allele G specific forward	5'ATGGTGTTAATCTCATCTGGTGGGC3'	312 bp
Common reverse	5'ATGCCCAACGGTCCAGAAATAC3'	312 bp

Figure-1, agarose gel electrophoresis was used for the presence of the PCR product.

Fig. 1: PCR Product of the *IL-17A* (2275913) G/A gene. Finding the Final Results with the UV Documentation System of Agarose Gel in 50 Volts for 30 minute with DNA Ladder (M) 100bp. the product size is 312 bp for alleles.

Statistical analysis:

Our investigation was done employing Statistical Package for the Social Sciences software, version 26 (IBM, SPSS, Chicago, Illinois, USA), and Microsoft Excel 2010 program. The mean of the investigated parameters compared between the two groups using t-Test; Chi-Square test was applied to compare between percentages; Differences among groups were analyzed using one-way ANOVA analysis of variance. The Results of all tests with p-values <0.05 (two-side) were considered to be statistically significant.

RESULTS

Table (2) shows the demographic data for study population (patients as well as controls). Age showed a significant increase (*p=0.0387*) in patients (57.04 ± 9.877) compared with control (53.36 ± 9.295); in the same context; both patients and healthy controls were divided into four age groups: 35–45, 46–56, 57–67, and 68–78. When comparing within-patient group the results showed statistically significant differences (p=0.0085), the high percentage of patients was in the age 57-67 at a rate of 38%. Regarding the distribution of the study population according to sex, there was no any statistical significance (*p=0.7598*) for sex in the development of the disease. The analysis of results showed that 34% of patients are smokers compared to 22% in the control group. The (*p= 0.0603*) suggested a trend towards statistically significant, but doesn't meet the traditional threshold of 0.05. Finally, according to severity of disease the diabetic patients were categorized into: mild, moderate, and severe; but the result of statistical analysis revealed No statistically significant difference (p=0.5945)

Table 2: Demographic data for study population

Parameters	**Study population No. (%)**		***P value***	
	Patients (n=50)	**Control (n=50)**		
Age (year) Mean ±S.D	57.04 ± 9.877	53.36 ± 9.295	0.0387*	
Age group	**Patients (n=50)**	**Control (n=50)**	**Total (n=100)**	***P value***
35–45	6 (12%)	9 (18%)	15 (15%)	0.0455*
46-56	17(34%)	21(42%)	38(38%)	0.2689^{NS}
57-67	19(38%)	17 (34%)	36(36%)	0.6153^{NS}
68-78	8 (16%)	3(6%)	11(11%)	0.0001*
P value	0.0085*	0.0039*		
Sex				
Sex	**Patients (n=50)**	**Control (n=50)**	**Total (n=100)**	***P value***	**ODD (CI95%)**
Male	34 (68%)	35 (70%)	69 (69%)	0.7598^{NS}	0.911 (0.5000- 1.6587)
Female	16 (32%)	15 (30%)	31(31%)		
Smoking habit					
	Patients (n=50)	**Control (n=50)**	**Total (n=100)**	***P value***	**ODD (CI95%)**
Yes	17(34%)	11 (22%)	28(28%)	0.0603^{NS}	1.8264 (0.974-3.424)
No	33(66%)	39 (78%)	72(72%)		
Severity					
Mild	15 (30%)		50	0.5945 ^{NS}	
Moderate	19 (38%)				
Severe	16 (32%)				

*Significant difference at the 0.05 level by chi-square test, T-test, and Odds ratio.
NS: Non-significant difference

The results in Table (3) showd that the majority 32 (64.0%) of diabetic foot ulcer patients had fore foot ulcer, while lowest percent (10%) of patients had mid foot ulcer, with statistically significant difference (p=0.0001).

According to the duration of disease the patients were divided into three groups: <10 years 16 (32%), 10-20 29 (58%), and >20 5 (10%); the significantly (*p=0.0001*) as shown in Figure (2).

The effect of the site of ulcer on some laboratory markers is illustrated in Table (4). The results of the statistical analysis showed significant differences in all studied laboratory markers except glucose and lymphocytes. Hba1c and ALT showed a significant increase in fore foot ulcer; Urea, Creatinine, WBC, and Platelets were significantly increased in hind foot ulcer, while AST was significantly decreased in hind foot ulcer. Triglyceride, Cholesterol, and LDL were significantly increased in all foot ulcers.

Table 3: Site of ulcer for diabetic foot ulcer patients

Site ulcer	Fore foot	Mid foot	Hind foot	All foot	*P value*
Count	32	5	7	6	0.0001*
%	64.0%	10.0%	14.0%	12.0%	
Total	50 (100%)				
*Significant difference at the 0.05 level by chi-square test.					

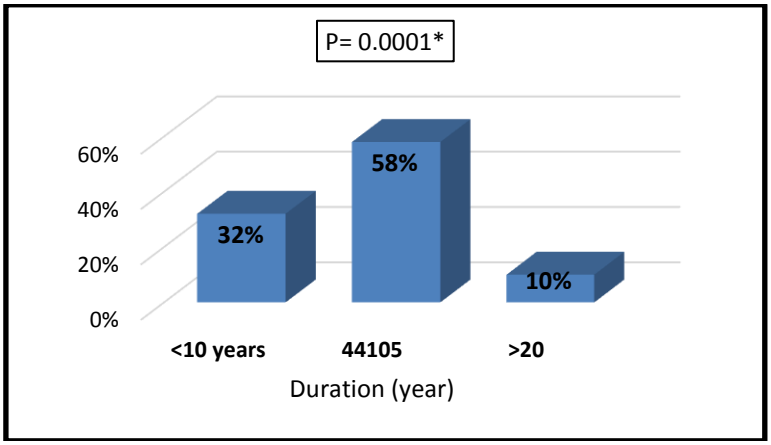

Fig. 2: Duration of Disease

Table 4: Laboratory markers for diabetic foot ulcer patients according to site of ulcer

Laboratory markers	Site of ulcer Mean ± Std. Deviation				P value	LSD value
	Fore foot (n=32)	Mid foot (n=5)	Hind foot (n=7)	All foot (n=6)		
Hba1c	11.253±2.3702 [a]	9.28±1.14 [c]	10.914±2.650 [ab]	10.483±2.147 [b]	0.0006*	1.01
Glucose	285.93±92.746	277.506±163.92	310.137±61.677	289.109±80.822	0.6127[NS]	49.90
Urea	37.215±27.323 [b]	25.862±4.049 [c]	42.335±14.177 [a]	36.390±9.312 [b]	0.0007*	7.88
Creatinine	0.875±0.505 [ab]	0.713±0.270 [c]	0.982±0.359 [a]	0.804±0.262 [b]	0.0204*	0.172
ALT	27.019±9.141 [a]	18.3±8.027 [c]	21.743±7.416 [b]	21.609±11.13 [b]	0.0013*	4.28
AST	25.657±5.473 [a]	26.033±5.008 [a]	19.282±3.428 [b]	24.256±8.514 [a]	0.0000*	2.75
Triglyceride	146.271±54.21 [b]	141.546±50.155 [b]	116.931±51.02 [c]	173.343±48.97 [a]	0.0001*	24.27
Cholesterol	160.221±29.40 [b]	171.534±18.889 [b]	148.709±16.31 [c]	190.656±68.56 [a]	0.0000*	17.88
LDL	74.546±20.231 [b]	91.478±18.467 [a]	64.596±15.023 [b]	94.140±42.324 [a]	0.0000*	11.96
WBC	8.823±2.101 [b]	7.446±0.529 [b]	10.109±5.26 [a]	8.565±2.33 [b]	0.008*	1.52
Lymphocyte	30.142±5.298	30.263±5.047	26.531±8.984	30.806±9.084	0.0844[NS]	3.64
Platelets	264.258±79.84 [b]	253.903±51.399 [b]	328.903±120.31[a]	265.29±44.59 [b]	0.0012*	40.48
NS: Non- significant difference, *Significant difference under p ≤ 0.05 by One way – ANOVA test, Different small letters refer to significant among groups.						

Table (5) displays genotypes and allele frequency for *IL-17A* gene in the study population. The statistical analysis for these genotypes yielded a p-value of 0.095, an odds ratio of 0.4394, and a confidence interval of 0.1675 to 1.1522. This result points out a trend towards a significant distribution for genotypes between diabetic foot ulcer patients and healthy control, but the difference isn't statistically significant at *0.05* thresholds. The odds ratio revealed a potential protective impact of GG genotype against this disease, although the wide confidence interval highlights uncertainty.

Regarding allele frequencies, in diabetic foot ulcers patients, for G allele the frequency is 42, for A allele the frequency is 28; in control group, G allele frequency is 55, A allele frequency is 15. The allele statistical analysis yields a p-value of 0.0187, odds ratio of 0.4091, and confidence interval of 0.1943- 0.8615, which demonstrated a significant difference in allele frequencies between diabetic patients and healthy individuals. The existence of G allele is correlated with lower risk for developing foot ulcer as compared with A ones, held up by the odds ratio and confidence interval, which don't include (1), suggesting a protective impact of G allele.

Table 5: *IL-17A* genotypes and allele frequency in studied groups

Genotypes	Diabetic patients (35)		Healthy control (35)		*P value*	ODD (CI95%)
	n	%	n	%		
GG	16	45.7143	23	65.7143	0.095^{NS}	0.4394 (0.1675 to 1.1522)
GA	10	28.5714	9	25.7143		
AA	9	25.7143	3	8.5714		
Alleles frequency						
G	42	60	55	78.5714	0.0187	0.4091 (0.1943 to 0.8615)
A	28	40	15	21.4286		
ODD: odds ratio, CI: confidence interval						

DISCUSSION

Our study shows that the mean of age of the study groups varied significantly (P=0.0387) in the current investigation. This result was consistent with research done by Zaki, *et al.* [15], which showed that the average age significantly influences the incidence of foot ulcers, gangrene, and amputations. It also matched with findings of another study done by McDermott, *et al.* [16] which showed that the probability of getting diabetic foot ulcers increases with age. The present investigation categorized both patients and healthy controls into four groups depending on age. Our study indicates that the group whose ages were (68-78) showed significant differences (*p=0.0001*), and this align with another study conducted by Rosinha, *et al.* [17] who showed significant differences regarding age, as there was a higher diabetic foot ulcers' frequency in the elderly. The research groups did not differ significantly in terms of sex (*P=0.7598*). This outcome was consistent with study accomplished by Niț ă, *et al.* [18] who reported there were no statistically significant differences between sexes. A study by Vahwere, *et al.* [19] which indicated that sex was not significantly linked with the severity of DFU. No significant changes (P=0.0603) were observed between the research groups regarding smoking. This result aligns with study conducted by Shahbazian, *et al.* [20] who reported that smoking lacked a significant correlation with the risk of diabetic foot ulcers, and a study done by Vahwere, *et al.* [19] that reported that smoking was not linked to the severity of diabetic foot ulcers, attributed to the relatively low number of smokers in the study. A possible explanation for the current study might be the sample size is too small, and confounding variables such as poor glycemic control and peripheral artery disease (PAD) have a stronger influence on DFU outcomes than smoking alone. In this study, diabetic patients were categorized into three severity groups: mild (30%), moderate (38%), and severe (32%). Statistical analysis revealed no significant differences among these groups (*P=0.5945*)., The number of moderate cases had a higher percentage compared to the mild and severe cases, and this is similar to study by Niț ă, *et al.* [18] , which revealed that 85.7% of all cases were moderate.

The current study has shown that there were significant variations (*P=0.0001*) in the patients' ulcer sites. The forefoot accounted for the largest percentage of injuries (64%) and it is in line with, a study done by Lee, *et al.* [21], who demonstrated the same result, where the highest percentage of cases in forefoot. Ulcers situated in the forefoot region have a higher risk factor for diabetic foot amputation than those located in the midfoot or hindfoot. Ellis, *et al.* [22] also found the majority of patients with diabetes or diabetes with peripheral artery disease (PAD) had forefoot ulcers.

According to duration of the ulcer, there were significant differences (*P=0.0001*) between patients in the current investigation. These findings concurred with

a study done by Almobarak, *et al.*[8], who discovered that having diabetes for more than ten years is linked to a 3.16 fold higher risk of developing diabetic foot. Diabetes foot complications are 1.73 times more likely to occur in people who have had the disease for more than 20 years. However, the adjusted effect of having diabetes for more than five years on the likelihood of developing diabetic foot was not statistically significant. Dekker, *et al.* [23] revealed that the length of time of diabetes is strongly correlated with diabetic foot ulcers, suggesting that individuals with poorly managed diabetes and prolonged illness duration may need increased monitoring for ulcers.

In the current study, HbA1C(*P=0.0006*) and ALT(*P=0.0013*) were significantly higher in forefoot ulcers compared to other sites . This result is in agreement with a previous study conducted by Katya, *et al.* [24]**,** demonstrated that HbA1c has been found to be strongly predictive of subsequent ulceration and amputation**.** compared to individuals without foot ulcers (NFU), Wang, *et al.* [25] showed that DFU patients had much higher blood ALT levels. In addition, urea(*P=0.0007*), creatinine(*P=0.0204*), white blood cells (WBC)(*P=0.008*), and platelet (PLT) (*P=0.0012*) were significantly higher in hindfoot ulcers. Similar findings were reported by Katya, *et al.* [24]**,** high significance of urea and creatinine among the studied groups (strongly predictive of subsequent ulceration and amputation). Also Gong, *et al.* [26] observed that amputated individuals had elevated levels of PLT and WBC count. On the other hand, AST(*P*=0.0000) was significantly decreased in hindfoot ulcers compared to other sites. In contrast to current study Wang, *et al.* [25] indicated that the blood ALT and AST levels in DFU patients were significantly higher when compared to non foot ulcer (NFU) patients. Moreover triglycerides(*P=0.0001*), cholesterol(*P=0.0000*), and LDL(*P=0.0000*) were significantly elevated across all ulcer sites. Hypercholesterolemia, LDL plasma level, and hypertriglyceridemia, were reported in diabetic foot patients, this study was conducted by a study of AbdAllah and Sharafeddin [27] who was identical to the current study.

According to our results association between *IL-17A* gene (rs2275913) polymorphism and DFU), revealed no statistically significant difference between healthy individuals and patients with diabetic foot ulcer in genotype frequencies of *IL-17A* gene (rs2275913) polymorphism (*P=0.095*, ODD= 0.4394, CI=0.1675 - 1.1522). The correlation of GG genotype appear as potential protective against diabetic foot ulcer (higher percentage appear in healthy control group 65.7143% than 45.7143% in patients group). This result was agreement with the study done by Motamed, et al. 13, The AA genotype of this polymorphism enhanced the chance of being at risk for recurrent miscarriage (RM), however, no statistically significant association was observed between the GG and GA genotypes of *IL-17A* rs2275913 and RM. Furthermore, Borilova Linhartova, *et al.* [28] found no significant differences in the *IL-17A* (rs2275913) genotype frequencies between the healthy groups and patients with Chronic Periodontitis(CP). And it was compatible with the study done by Pk and Kumaran [14], which revealed no significant alteration in the genotype distribution between healthy controls and CP patients with or without T1DM.

The *IL-17A* polymorphism including the A allele exhibited significant variations in allele frequencies between DFU patients and healthy persons (P=0.0187, ODD=0.4091, CI=0.1943 - 0.8615) . Diabetic foot ulcer patients had greater rates of the *IL-17A* rs2275913 gene polymorphism's allele A and homozygous genotype AA than healthy people. In return, it was lower risk for developing foot ulcer with frequencies of the allele G (protective allele). This result was consistence with the study done by Ponce-Gallegos, *et al.*[29] who revealed there was a significant difference found for the AA genotype of rs2275913 polymorphism when comparing chronic obstructive pulmonary disease (COPD) with healthy subjects , and the A allele was also associated with the presence of COPD related to tobacco smoking , Nazarian, *et al.* [12] also discovered that diabetic patients with nephropathy had greater rates of the *IL-17A* gene polymorphism's allele A and genotype AA than healthy people.

Unfortunately, no research has been done on the *IL-17A* rs2275913 gene polymorphism in diabetic foot ulcers to compare with the current study. Furthermore, individuals with AA genotypes that is, genotypes containing the A allele had a much greater rate of DFU. Accordingly, the homozygous (mutant) genotype AA was more common in DFU than the GG genotype and G allele. This suggests that patients with diabetic foot ulcers may be at risk for this genotype (AA).

CONCLUSION

The findings of this study have demonstrated that the genotype (AA) and allele (A) of *IL-17A* gene (rs2275913) polymorphism maybe have a role as risk factor for diabetic foot ulcer. To show the role of this polymorphism in diabetic foot ulcer patients, more studies with higher sample numbers are needed.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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