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Original Research

Interleukin-6 serum level and gene polymorphism in keloid patients

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Abstract: The formation of keloid is associated with accumulation of extracellular matrix (ECM) formed mainly of collagen and fibronectin. Persistent deregulated IL-6 synthesis causes the development of various diseases. This study aim to investigate interleukin 6 (IL-6) serum level and gene polymorphism in a sample of Egyptian patients having keloid. This study was carried out on 90 subjects; 60 patients with keloid, and 30 age and sex matched apparently healthy control. All subjects underwent full history taking, clinical examinations, weight and length measuring to calculate BMI, dermatological examination, analysis of IL6-572 gene polymorphism using REFLP- PCR and IL-6 serum level using ELISA.IL-6 serum levels were significantly higher in keloid patients than control group (75.54±39.18) vs (19.17±6.06), (p <0.001). The higher serum levels of IL-6 were associated with GG genotype (104.84±19.12) followed by CG (57.64±35.38) genotype (P<0.001). GG genotype was significantly higher in keloid patients and increased the risk for keloid development by nearly14 folds (p<0.001, OR (95%CI) =13.81). CG genotype was significantly observed in keloid patients and increased the risk for keloid development by about 4 times (p=0.010, OR (95%CI) =4.27). G Allele significantly increased the risk for keloid development by about 5 folds (P <0.001 OR =5.11). In conclusion, there was a great association between IL-6 572 gene polymorphism and its serum level in patients with keloid specifically who have family history.

Key words: Interleukin; Keloid; Polymorphism; PCR; Collagen.

Introduction

Keloid and hypertrophic scars are represented by unnecessary accumulation of collagen in the dermis and subcutaneous tissues optional to careful wounds. These difficult sores, cause different complexities and enthusiastic issues like diminished confidence, self-perception, and personal satisfaction, hypertrophic consume scars related with torment, tingling, and decreased scope of movement Although keloids are not harmful to our health, they may present cosmetic concerns (1).

Keloid and hypertrophic scar result from skin injury, for example, surgeries, inoculations, diseases, bug chomps, consumes, body puncturing, inking, and any procedure that outcomes in skin irritation (skin inflammation, folliculitis). Keloid is also defined as an abnormal raised, ill-defined scar that grows beyond the boundary of the original site of a skin injury and is characterized by a flattened and smooth appearance with the size of tumor with different shapes and sizes (2).

Interleukin-6 (IL-6) is a pleiotropic cytokine with a wide scope of natural exercises. It is basically created at locales of intense and incessant irritation, where it is discharged into the serum and initiates a transcriptional provocative reaction through Il-6 receptor alpha. The IL-6 gene is located on chromosome 7p21, and is composed of 6 exons. There are several polymorphisms in the promoter region of the IL-6 gene which are 597G/A, 572G/C, and 174G/C. Of these polymorphisms, the two most commonly involved and researched are -174 G > C and-572 C > G. Both of these polymorphisms are reported to influence the transcription rate of IL-6 (3).

Elective names for IL-6 are IFN-2 (IFNB2), B-cell separation factor, B cell stimulatory factor 2 (BSF2), hepatocyte stimulatory factor, and hybridoma development factor (4) and (5).

Keloid and keloid scare are disfiguring problem and might hinder the movement of joints if they develop on them, and malignant transformation might occur. So, studies should be done to clarify the biochemical and genetic bases of them. The present investigation aim to reveal insight into the role of IL-6 in aetiopathogenesis of keloid through assessment of its serum level and its polymorphism 572G/C in keloid patients.

Materials and Methods

This case-control study was directed on 60 patients (patient group) with keloid, and 30 age and sex apparently normal subjects (control group). Cases were chosen from the Dermatology outpatient center at Menoufia University Hospital. The lab work portion of the study

was done at the Biochemistry department, Faculty of Medicine, Menoufia University.

The investigation convention was affirmed by the moral advisory group of Faculty of Medicine, Menoufia University that was as per Helsinki Declaration in 1975 (reconsidered in 2000). Aconsent was gotten from all subjects involved in the study.

Patients who had keloid due to skin disorders, hypertrophic scar syndrome, genetic or chromosomal disorders were excluded from this study.

Each member was exposed to full history taking, clinical examinations, weight and length estimating to ascertain BMI(6) and dermatological examination including, appraisal of site(e.g. face, neck, leg, mid-region), size and term of keloid. Vancouver scar was first depicted by Sullivan in 1990, which was the most perceived consume scar scale that was used to evaluate keloid seriousness. Examination of IL6-572 (rs2228145) polymorphism using REFLP-PCR and IL-6 serum levels utilizing ELISA were performed for all members.

Sampling

Under total aseptic condition, 5 ml of venous blood were withdrawn from each subject after a night fasting and isolated into 2 sections. The initial segment 2.5 ml was moved into a plain tube, left at37ºC for 30 min to clump at that point centrifuged for 10 min at 4000 r.p.m. The serum got was kept in - 80°C till time of measuring of IL-6 serum level utilizing ELISA. The other 2.5 ml of blood test was moved into EDTA tube and kept in - 20 ºC for DNA examination utilizing Restriction Fragment Length Polymorphism PCR (RFLP-PCR).

IL6-572 genotyping

DNA extraction was performed utilizing Zymo Research Quick-g DNA smaller than normal prepGenomic DNA purging pack (USA). DNA was eluted and put away at - 20 ºC for further PCR method.

REFLP examination of IL-6-572 (rs2228145) gene polymorphism:

PCR analysis was performed using proper primers for the IL-6-572 polymorphic area. Forward primer 5'-GGAGACGCCTTGAAGTAACTGC-3' Reverse primer 5'-GAGTTTCCTCTGACTCCATCGCAG-3'.A total volume of 0.5 ug/lL of genomic DNA sample obtained from the peripheral leucocytes was added into the reaction mixture. The mixture also included 0.5 umol/L forward primer, 0.5 umol/L reverse primer, 0.2 umol/L dNTP, 1.5 umol/L MgCl2, 10 • PCR buffer, 0.025 units /lL taq DNA polymerase. Totally 50 lL of PCR volume was used in the study. The procedure denaturation at 95 C for 3 min and 94 C for 45 s, annealing at 57 C for 45 s, extension at 72 C for 1 min in a total of 30 cycles with a waiting period for 10 min at 72 C in stepwise manner. Samples were kept at 4 C until the analysis time. Digestion of the amplified product was done using FastDigest®FOK1 enzyme supplied by THERMO SCIENTIFIC, EU/Lithuania. Working Solution for FastDigest was prepared and incubated at 37°C For 60 minutes (Hutchinson et al., 2000); Water nuclease-free 6.5 µl, 10X FastDigest® Buffer 2.5 µl, PCR product 15 µl, FastDigest®FOK1 enzyme 1 µl with total volume of 25 µl. The amplified fragments of DNA were separated in 2% agarose gel containing ethidium bromide.

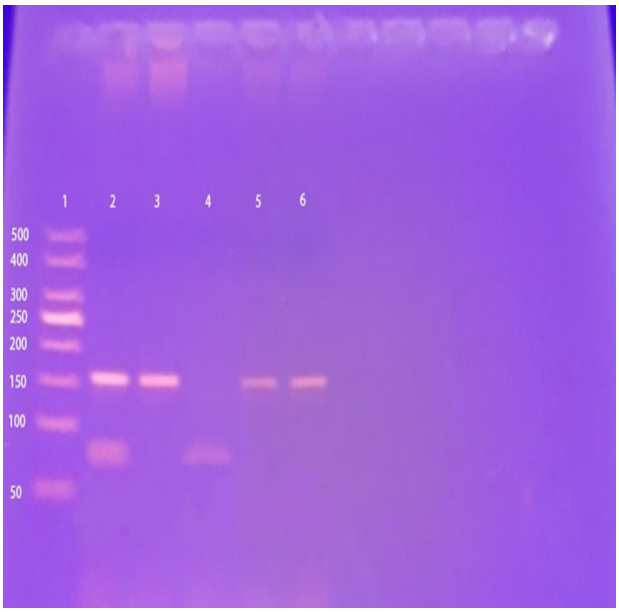

Figure 1. Photograph of RFLP-PCR product of IL-6 SNP-572 G>C run on 2% agrose gel. A 50 bp marker DNA is used in lane 1. Lane 2 showing 2 bands at 154 bp and band below 100bp. Lane 3,4,5 remain uncut showing band at 154bp.

Serum interleukin concentration was measured by Kits supplied by AviBion Human IL-6 ELISAKit (Orgenium Laboratories).

Statistical analysis

Results were collected, tabulated and statistically analyzed by IBM personal computer and statistical package SPSS version 20 (SPSS Inc., Chicago, U.S). Hardy-Weinberg equilibrium was computed to exclude any bias of results. Qualitative data were described using number and percent, while quantitative data were expressed in mean ± SD. Student t-test was used for comparison between two groups having quantitative variables. Mann Whitney and Kruskal–Wallis tests were used for comparison of two and three groups of non-parametric variables respectively. P-value < 0.05 was considered statistically significant.

Results

Table 1 shows a non-significant differences between the studied groups regarding their age (P=0.092), gender (P= 0.881), smoking (P= 0.754) and BMI (P=0.234).

Table 2 shows clinical characteristics of keloid patients. More than half of patients had positive family history of keloid (38, 6.3%). The most prevalent site of keloid was the limbs (28, 46.7%) followed by trunk (24, 40%) and the least affected site was head and neck. Half of the cases developed keloid post operatively (30, 50%).Vancouver scale score had a Mean ± SD of 6.38±2.88, a median of 7 and a range of 3-12.

Table 3 shows IL-6 serum levels of studied groups: The mean IL-6 serum levels were significantly higher in keloid patients than control group (75.54±39.18ng/ml vs 19.17±6.06ng/ml), (p <0.001).

Table 4 shows that there was a significant difference between the mean values of serum IL-6 levels as regards different genotypes of the corresponding gene. The higher levels were associated with GG genotype (104.84±19.12) followed by CG (57.64±35.38) geno-

Table 1. Demographic characteristics of keloid patients and control group.

Demographic characteristics	Patients (n=60)	Controls (n=30)	Test of significance	P- value
Age (years)				
Mean ± SD	32.28±13.51	37.70±15.55		
Median	30	40	Mann-Whitney=1.70	0.092
Range	11-65	10-65		
Sex: [No (%)]				
Males	29 (48.3)	15 (50.0)	χ^2=0.02	0.881
Females	31 (51.7)	15 (50.0)		
Smoking: [No (%)]				
Smokers	20 (33.3)	11 (36.7)	χ^2=0.10	0.754
Non-smokers	40 (66.7)	19 (63.3)		
BMI:				
Mean ± SD	29.73±3.84	28.64±4.45		
Median	29.7	29.8	t=1.20	0.234
Range	18.6-38.8	21.3-38.1		
Family history: [No (%)]				
-Present	38 (63.3)			
-Absent	22 (36.7)			

BMI=Body mass index.

Table 2. Clinical characteristics of keloid patients.

Clinical characteristics	Patients (n=60)
Site of lesion: [No (%)]	
-Head & neck	8 (13.3)
-Trunk	24 (40.0)
-Limbs	28 (46.7)
Duration of disease (years):	
-Mean ±SD	2.57±1.59
-Median	2
-Range	6 moths-7 years
Vancouver scale score:	
-Mean ±SD	6.38±2.88
-Median	7
-Range	3-12
Vancouver scale score classifications: No (%):	
-Mild (0-3)	13 (21.7)
-Moderate (4-7)	24 (40.0)
-Severe (8-11)	23 (38.3)
Precipitating factors: [No (%)]	
-Spontaneous	5 (8.3)
-Operation	30 (50.0)
-Burn	25 (41.7)

Table 3. IL-6 serum levels between the two studied groups.

IL-6	Patients (n=60)	Controls (n=30)	Mann Whitney test	P- value
IL-6 serum levels (ng/ml)				
Mean ± SD	75.54±39.18	19.17±6.06	6.84	<0.001*
Median	77.0	17.1		
Range	12.7-177.8	13.4-37.0		

* p<0.05 is considered statistically significant.

Table 4. Expression of IL-6 -572G/C gene polymorphism as regards IL-6 serum levels in keloid patients.

Items	IL-6-572G/C gene polymorphism in keloid patients			Kruskal-Wallis test	P- value
	CC (n=10) Mean± SD	CG (n=19) Mean± SD	GG (n=31) Mean± SD		
IL-6 serum levels (ng/ml) by ELISA	28.14±11.48	57.64±35.38	104.84±19.12	37.78	P<0.001* P1= 0.011* P2= <0.001* P3= <0.001*

* p<0.05 is considered statistically significant.

Table 5. Distribution of IL-6-572G/C gene polymorphism and allele frequencies in keloid patients and control group.

IL-6 gene polymorphism	Patients (n=60) No (%)	Controls (n=30) No (%)	χ^2	P- value	OR (95% CI)
Alleles					Reference
CC	10 (16.7)	18 (60.0)	19.80		
CG	19 (31.7)	8 (26.7)		0.010* (CG vs CC)	4.27 (1.38-13.25)
GG	31 (51.7)	4 (13.3)		<0.001* (GG vs CC)	13.81 (3.81-51.03)
Alleles	**(n=120)**	**(n=60)**			
C	39 (32.5)	44 (73.3)	26.84	<0.001*	5.11 (2.87-11.36)
G	81 (67.5)	16 (26.7)			

OR: Odd's ratio. * p<0.05 is considered statistically significant**.**

Table 6. Expression of IL-6-572G/C gene polymorphism as regards demographic and clinical data in keloid patients.

Items	IL-6 gene polymorphism in keloid patients			Kruskal-Wallis test	P- value
	CC (n=10) Mean± SD	CG (n=19) Mean± SD	GG (n=31) Mean± SD		
Age (years)	43.10±13.71	27.10±9.88	32.31±13.88	8.92	0.012* P1= (0.005*)
BMI	30.52±2.92	29.17±4.01	29.87±4.04	0.98	0.613
Duration of disease (years)	2.55±1.64	2.61±1.47	2.55±1.72	0.15	0.926
Vancouver scale score	3.40±1.26	5.10±2.83	8.34±1.70	28.57	<0.001* P1=(<0.0*) P2=(<0.0*)
Sex:	**No (%)**	**No (%)**	**No (%)**	**χ2**	
-Males	8 (80.0)	8 (421)	13 (41.9)	4.82	0.090
-Females	2 (20.0)	11 (57.9)	18 (58.1)		
Site of lesion:					
-Head & neck	0	4 (21.1)	4 (12.9)	2.84	0.584
-Trunk	5 (50.0)	6 (31.6)	13 (41.9)		
-Limbs	5 (50.0)	14 (45.2)	14 (45.2)		
Precipitating factors:					
-Spontaneous	0	1 (5.3)	4 (12.9)	2.1	0.717
-Operation	5 (50.0)	10 (52.6)	15 (48.4)		
-Burn	5 (50.0)	8 (38.7)	12 (38.7)		
Family history:					
-Present	7 (70.0)	8 (42.1)	7 (22.6)	7.68	0.022*
-Absent	3 (30.0)	11 (57.9)	24 (77.4)		

P1: CC vs CG. P2: CC vs GG. * p<0.05 is considered statistically significant.

type (P<0.001). Also, by using multiple comparison test, both GG and CG genotypes had significantly higher IL-6 levels than CC genotype (P=0.011, P <0.001) respectively, and GG genotype had significantly higher IL-6 levels than CG genotype (p< 0.001)

Table 5 shows that IL-6572G/C genotype CG genotype was significantly observed in keloid patients and increased the risk for keloid development by about 4 times (p=0.010, OR=4.27). Also, GG genotype was significantly higher in keloid patients and increased the risk for keloid development by nearly14 folds (p<0.001, OR=13.81). Moreover, G Allele significantly increased the risk for keloid development by about 5 folds (P <0.001 OR =5.11)

Table 6 shows that there was a statistical significant associations between IL-6572G/C genotype regarding age of patients (P=0.012), vancouver scale score (P<0.001), smoking (P=0.052), and family history (p0.022) in keloid patients. Regarding Vancouver scale score (VSS), CG and GG genotype carriers had significant higher VSS mean values (5.10±2.83 and 8.34±1.70) , (P1=<0.001, P2=<0.001) respectively. Additionally, IL-6 CG genotype was significantly predominate in young age group than CC genotype (P=0.005). However, IL-6 CC genotype was significantly associated with positive family history (P=0.002).

Discussion

The exact aetiology of keloid and hypertrophic scars are not understood, but most likely entails genetic and environmental factors. An abnormal composition and metabolism of collagen in hypertrophic scars and keloids were demonstrated (7). Spontaneous keloids may arise without a history of trauma to a particular site (8,9).

Interleukin-6 (IL-6) is a glycoprotein with 21–26 kDa consisting of 212 amino acids. It is a proinflammatory and immunoregulatory cytokine contributing to host defense against infections and tissue injuries. Persistent deregulated IL-6 synthesis causes the development of various diseases (10). Moreover, the formation of keloid is associated with accumulation of extracellular matrix (ECM) components mainly of collagen and fibronectin (11)

To the best of our knowledge, this study may be the first one that investigates interleukin 6 (IL-6) serum level and gene polymorphism in a sample of Egyptian patients having keloid aiming to shed light on their possible role in aetiopathogenesis of keloid.

To elucidate our aim we selected 60 cases suffering from keloid from those attending the Outpatient Clinic of Dermatology and Andrology department, Menoufia University Hospitals and 30 apparently healthy individuals as control group. For all, IL-6 serum levels using ELISA plus IL-6 polymorphisms by REFLP-PCR respectively.

In the current study, there was a non-significant statistical difference between the studied groups regarding their age. These results was not alongside with Marneros et al., (12) who reported that keloid can occur at every age but is more prevalent between the ages of 10 and 30 and explained his results by this hypothesis; which focus on the influence of hormones on keloid formation. Such hypothesis is based on the observation that keloids occur commonly between ages 10 and 30 years, at which time plasma levels of growth hormone and insulin like growth factor 1 (IGF-1) are also high. The involvement of the activated IGF-1/IGF-1 receptor axis in the pathogenesis of the increased activity of fibroblasts has previously been suggested and increased androgen binding in keloids has been demonstrated.

In this study, positive family history of keloid was reported in 63.3% of our studied cases. There were many supporting evidence that genetic factors play a major role in determining susceptibility to keloid (13,14). In agreement with our study Alexander et al., (13) who reported that some keloid cases are familial. A hereditary component in keloid etiology has been considered, mainly based on the higher occurrence in darker-skinned races. In the present work, the studied population included 29 males and 31 females The difference in occurrence based on sex has not been demonstrated convincingly. Although, some epidemiological studies have shown that more keloid patients are female (15). This might be explained by greater cosmetic concerns about keloids in female individuals than in male, and by the greater frequency of ear piercing in females. However, another study show equal incidence of keloids in male and female subject according to Ketchum et al., (16).

In the present study, we examined the circulating IL-6 serum levels in keloid cases. We reported a statistically significant increase in serum IL-6 level mean values in keloid patients than their matched peers ($p<0.001$). In agreement with our finding Zhu et al., (17) who revealed a statistical significant elevation of serum IL-6 levels in their study on 224 Chinese keloid patients compared with the controls.

IL-6 is a 27 kDa glycoprotein that is composed of 184 amino acids, and is secreted by activated inflammatory cells such as lymphocyte and macrophage cells (18). It has been confirmed that IL-6 is involved in many metabolic processes, such as tumor growth, differentiation, and regulation of the immune microenvironment (19). IL-6 plays a role in a variety of biological functions by activating multiple signaling pathways. For example, it activates the Ras/Raf/MEK/ERK1/2 pathway to promote tumor cell proliferation (20,21,22)

In this current study we investigated IL-6-572G/C gene polymorphism ,we found a statistical significant differences between the different genotypes and alleles of IL-6-572G/C polymorphism among the studied groups. Comparing the wild IL-6-572G/C genotype (CC), (CG) genotype was significantly observed in keloid patients and increased the risk for keloid development by about 4 times. Also, GG genotype was significantly higher in keloid patients and increased the risk for keloid development by nearly14 folds. Moreover, G Allele significantly increased the risk for keloid development by about 5 folds. In agreement with our finding,(16) investigated 170 Japanese patients with keloids and 100 unaffected healthy subjects, they observed significant link between IL-6-572G/C polymorphism and keloid(23).

In this study, IL-6 G/G genotype was associated with enhanced transcriptional activity and demonstrated significantly elevated IL-6 serum levels than C/C and C/G genotypes that could explain the current observed significant association of IL-6-572G/G genotype with severe form of keloid ($p<0.001$). In accordance with our finding, Zhu et al., (17) had observed direct functional effect of IL-6-572G/G genotype on circulating IL-6 serum level and its association with keloid severity.

The *IL-6* gene is located on chromosome 7p21, and is composed of 6 exons. There are several polymorphisms in the promoter region of the *IL-6* gene. Of these polymorphisms, the two most commonly involved and researched are -174 G > C and-572 C > G. Both of these polymorphisms are reported to influence the transcription rate of *IL-6* (24)

In our current study we found a significant statistical difference regarding family history and this was in agreement with Zhu et al.,(17). Many studies have demonstrated that KS is familial in nature, and reported its presence in identical twins which add a genetic component to its disease pathology (12, 25).

According to our results, there was a great association between IL-6 572 gene polymorphism and its serum level in patients with keloid specifically who have family history. We think that these results may have influence on methods of treatment of Keloids by interfering with IL-6 signaling pathway. We recommend further investigations on a large number of patients.

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