Role of KruPPel Like Factor (2) in Pathogenesis of Inflammatory Acne

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Abstract

Skin break out vulgaris (AV) is a constant inflammatory skin infection that creates around the pilosebaceous contraption. Aggravation assumes a focal part in skin inflammation pathogenesis. The provocative changes advance Propionibacterium skin inflammation (P acnes) abundance through both inborn and versatile insusceptible initiation. It is entrenched that the emission of proinflammatory cytokines, for example, IL-1, IL-8, TNF-α and MMPs adds to the provocative idea of skin break out. KruPPel like factor 2 (KLF2) is end up being a negative controller of aggravation and NFkB movement through a significant raised articulation levels of IL-1, IL-6, TNFα and MMPs. To survey part of KLF2 in pathogenesis of provocative skin break out and its connection to skin inflammation seriousness and example of recuperating of skin inflammation injury, serum level of KLF2 mRNA was estimated in 100 skin inflammation patients and 50 age and sex coordinated sound subjects as control by utilizing quantitative continuous polymerase chain response (qRT-PCR). The mean estimation of KLF2 was lower in skin inflammation bunch than in the benchmark group (P <0.001). The mean estimation of KLF2 was lower in fiery skin break out gathering than in the non-incendiary skin break out gathering (P<0.001). KLF 2 was lower in cases recuperated by scarring than in cases mended by post provocative hyper pigmentation (P=0.016). KLF2 might be a defensive factor against skin inflammation improvement, seriousness and scarring.

Keywords: KLF2, Acne Vulgaris, Inflammatory cytokines.

1. Introduction

Skin inflammation vulgaris is an ongoing provocative skin infection including pilosebaceous follicles. It is ordinarily ordered into two gatherings: non-incendiary (open and shut comedones) and fiery (papules and pustules). Skin inflammation normally starts in youth nonetheless, it regularly endures into adulthood [1].

As per the Global Burden of Disease (GBD) study, skin inflammation vulgaris influences ~85% of youthful grown-ups matured 12–25 years [2] .

The pathogenesis of skin inflammation vulgaris is an intricate cycle wherein a few variables have been ensnared including unreasonable androgenic incitement and sebum discharge, unusual separation, multiplication and hyper-keratinisation. These cycles lead to impediment of the follicular orifice and resulting hypercolonisation by P. skin break out bacterium and inflammation [3].

The resistant framework underlies the inflammatory reason for skin break out pathogenesis. Skin explains dissolvable variables (counting suPPlement factors, antimicrobial peptides, chemokines and cytokines). The enactment of Toll like receptor 2 (TLR2) by P. skin break out prompts arrival of inflammatory cytokines, for example, IL-1, IL-6, IL-8, IL-10, IL-12 and TNFα that initiate aggravation and scar arrangement [4].

Mammalian KrüPPel like record factors have picked up acknowledgment as basic controllers in cell multiplication and separation during typical advancement just as in numerous infection states. The term "KrüPPel" is a German word importance "criPPle." This depends on the perception that Drosophila incipient organisms homozygous for

KrüPPel show changed thoracic and foremost stomach fragments [5].

KrüPPel like factor 2 was named for its high articulation in lung and has involved as a negative controller of irritation. KLF2 forestalls proinflammatory monocyte enactment and macrophage cell development by means of restraint of NFkB. KLF2 has additionally been ensnared in adipogenesis, foundational microorganism recharging and erythropoiesis [6].

KLF2 is likewise ensnared in the negative guideline of cell resistance by hindrance of initiation, separation and bond of T cells and monocytes. KLF2 interceded restraint of NFKB flagging prompts the concealment of cell reaction to the suPPortive of provocative cytokines IL-1 and TNFα and results in the lessening of fiery cycles [7]. Which may recommend the connection among KLF2 and pathogenesis of incendiary skin inflammation.

The point of the investigation is to survey the function of KLF2 in pathogenesis of provocative skin break out and to separate between incendiary skin break out and non-fiery skin inflammation as respects KLF2.

2. Patients and methods

This case control study was conducted on 50 patients diagnosed as inflammatory acne vulgaris ,50 patients diagnosed non-inflammatory acne vulgaris. In addition, 50 aPParently healthy individuals age and sex matched was chosen as control group. Patients were recruited from the outpatient clinic of Dermatology and Andrology Department of Benha university hospitals .

The study was aPProved by the local ethics committee on research involving human subjects of

Benha Faculty of Medicine. Informed consent was obtained from each individual before sample collection .

2.1 Inclusion Criteria

Patients with skin type I, II, III, IV and V. Different degrees of severity of acne vulgais according to global acne severity scale aged 18-35 years.

2.2 Exclusion criteria

Subjects having a significant concurrent illness, such as diabetes, epilepsy, lupus or congestive heart disease. Subjects having symptoms of a hormonal disorder. Subjects currently using immunosuPPressive medications. Subjects who are on systemic treatment for acne and pregnant subjects.

All patients were subjected to full history taking, complete clinical examination and Acne was assessed and graded using Global Acne Severity Scale [8]. KLF2 gene expression (KLF2 mRNA) was measured by real-time polymerase chain reaction (RT-PCR).

2.3 Statistical analysis

Information were taken care of to the PC and investigated utilizing IBM SPSS programming bundle adaptation 20.0. (Armonk, NY: IBM Corp) Qualitative information were depicted utilizing number and percent. The Kolmogorov-Smirnov test was utilized to confirm the ordinariness of conveyance Quantitative information were depicted utilizing range (least and greatest), mean, standard deviation, middle and interquartile range (IQR).

Noteworthiness of the got outcomes was decided at the 5% level. Chi-square test was utilized for clear cut factors, to look at between changed gatherings. F-test (ANOVA) was utilized for typically disseminated quantitative factors, to think about between multiple gatherings, and Post Hoc test (Tukey) for pairwise examinations. Mann Whitney test was utilized for strangely circulated quantitative factors, to think about between two considered gatherings. Understudy t-test was utilized for typically aPPropriated quantitative factors, to analyze between two examined gatherings. Collector working trademark bend (ROC) is created by plotting affectability (TP) on Y hub versus 1-particularity (FP) on X pivot at various cut off qualities. The region under the ROC bend signifies the demonstrative execution of the test. Territory over half gives worthy execution and zone about 100% is the best exhibition for the test. The ROC bend likewise permits an examination of execution between two tests. Cut off worth was picked utilizing Youden record head. Positive Predictive worth (PPV) is the likelihood of the sickness being available, among those with positive indicative test outcomes. Negative Predictive worth (NPV) is the likelihood that the sickness was missing, among those whose demonstrative test outcomes were negative.

3. Results

The present study included 100 patients with AV (50 inflammatory acne, 50 non-inflammatory acne), and 50 healthy control groups. Demographic data in all studied groups in Table (1).

Table (1) Comparison between the three studied groups according to demographic data**.**

	Inflammatory acne (n = 50)		Non-inflammatory acne (n = 50)		Control (n = 50)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	19	38.0	21	42.0	26	52.0	χ^2=2.11	0.348
Female	31	62.0	29	58.0	24	48.0	0	
Age (years)								
Min. – Max.	18.0 –32.0		18.0 –35.0		18.0 –35.0		F=9.835	<0.001[*]
Mean ± SD.	22.50 ± 3.62		26.08 ± 4.91		25.84 ± 4.89		[*]	
Median (IQR)	21.0 (20.0 –25.0)		26.0 (22.0 –30.0)		25.0 (22.0 –30.0)			
Sig. bet. groups	p_1<0.001[*], p_2=0.001[*], p_3=0.962							

χ^2:Chi square test F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)   p: p value for comparing between the studied groups
p_1: p value for comparing between inflammatory acne and non-inflammatory acne
p_2: p value for comparing between inflammatory acne and Control
p_3: p value for comparing between non-inflammatory acne and Control
*: Statistically significant at $p \leq 0.05$.

There was no statistically significant difference between inflammatory acne group, non-inflammatory acne group and the control group as regards sex of cases (P=0.348). But there was statistically significant difference between the groups as regards age of the cases (P=0.001) Table (1).

Table (2) Comparison between the three studied groups according to KLF2.

KLF2	Inflammatory acne (n = 50)	Non-inflammatory acne (n = 50)	Control (n = 50)	F	p
Min. – Max.	0.15 – 0.76	0.67 – 1.08	0.88 – 1.17	578.639[*]	<0.00
Mean ± SD.	0.27 ± 0.16	0.95 ± 0.09	1.0 ± 0.09		1[*]
Median (IQR)	0.20 (0.16 – 0.28)	0.96 (0.89 – 1.03)	0.98 (0.93 – 1.09)		
Sig. bet. Groups.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.082$				

F: F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey)

p: p value for comparing between the studied groups. p_1: p value for comparing between inflammatory acne and non-inflammatory acne. p_2: p value for comparing between inflammatory acne and Control.

p_3: p for comparing between non-inflammatory acne and Control. *: Statistically significant at $p \leq 0.05$.

There was statistically significant difference between the three study groups as regards KLF2 ($P<0.001$). The mean value of KLF2 was lowest in inflammatory acne group (0.27), rising (0.95) in non-inflammatory acne group and highest in the control group (1.0) Table (2).

Receiver Operator Characteristic curve (ROC curve) showed that the KLF2 was 98% sensitive and specific for prediction of inflammatory acne, KLF2 level was statistically signification for prediction of inflammatory acne cases ($P<0.05$) ,probability of inflammatory acne among those with low KLF2 level is 98% (*PPV* 98) and that cut off point of KLF2 for prediction of inflammatory acne is ≤0.67 Table (3) and Fig (1)

Table (3) Agreement (sensitivity, specificity) for KLF2 to diagnose inflammatory acne cases.

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
KLF2	0.999	<0.001[*]	0.995 – 1.0	≤0.67	98.0	98.0	98.0	98.0

AUC: Area Under a Curve , p value: Probability value, CI: Confidence Intervals,
 NPV: Negative predictive value, PPV: Positive predictive value

*: Statistically significant at p ≤ 0.05Cut off was choosed according to Youden index.
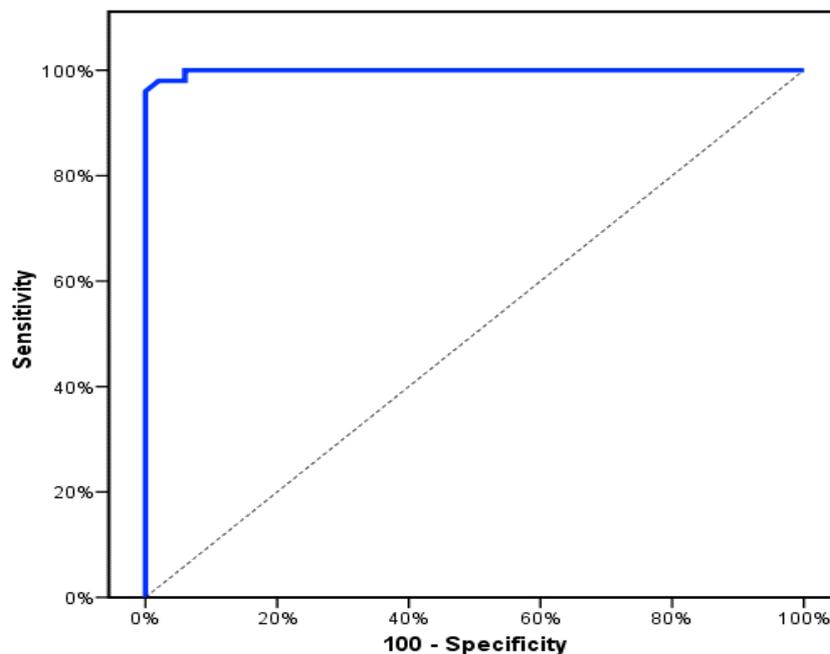
Fig (1) ROC curve for KLF2 to diagnose inflammatory acne cases

Table (4) Relation between KLF2 and different parameters in each group (n = 50).

				KLF2				
		Inflammatory acne				**Non-inflammatory acne**		
	N	Mean ± SD.	Test of Sig.	p	N	Mean ± SD.	Test of Sig.	p
Grading								
I	0	–	F=11.215[*]	<0.001[*]	29	0.96 ± 0.08	t=1.099	0.277
II	0	–			21	0.93 ± 0.11		
III	7	0.48 ± 0.24			0	–		
IV	11	0.29 ± 0.15			0	–		
V	32	0.22 ± 0.10			0	–		
Healing								
PIH	15	0.37 ± 0.20	t=2.663[*]	0.016[*]	35	0.96 ± 0.10	t=1.017	0.314
SCAR	35	0.23 ± 0.12			15	0.93 ± 0.09		

F: F for ANOVA   test t: Student t-test
p: p value for association between KLF2 and different parameters.

There was statistically significant difference in KLF2 as regards the Global Acne Grading System in inflammatory acne group (P<0.001) but this difference was not statistically significant in non-inflammatory acne group (P=0.277). There was statistically significant difference in KLF2 as regards

pattern of healing in inflammatory acne group (P=0.016), similarly KLF2 mean value was lower in cases healed by scars than those healed by post-inflammatory hyperpigmentation (PIH) in non-inflammatory acne group but this difference was not statistically significant (P=0.314).

4.Discussion

Skin inflammation is a constant incendiary skin infection including pilosebaceous follicles, it is normally ordered into two gatherings: non provocative (open and shut comedones) and fiery (papules and pustules) [1].

Skin break out pathophysiology is multifactorial with hyper-seborrhea and dyseborrhea, changed keratinization of the sebaceous conduit, P.acne colonization and aggravation all assuming a significant job. Adding to the unpredictability are changes in sebum creation, excessive touchiness to androgen creation and provocative cytokines influenced by the intrinsic invulnerable framework [9].

Significant levels of IL1, macrophages and CD4 cells in patients with skin inflammation contrasted and skin of those without skin inflammation recommend that aggravation goes before hyperproliferation in the advancement of skin inflammation [10].

KrüPPel like elements are individuals from the zinc-finger group of record factors named after their closeness to the Drosophila hole quality KrüPPel, the utilization of mathematical terminology for the 17 part KrüPPel family depends on the sequential request of their disclosure, for example, KLF1, KLF2, KLF3 [11].

KruPPel like factor 2 (situated at chromosome 19 p13.1) assumes significant part in directing adipogenesis and fiery sickness conditions, for example, rheumatoid joint inflammation, vascular illnesses, ongoing contaminations and malignancies. The KLF2 is communicated in single positive CD4 and CD8 cells and remains profoundly communicated in both credulous and memory T cells. It has been indicated that during T cell incitement, both KLF2 m-RNA and protein are down controlled. KLF2

additionally keeps up the practicality of T cells in the fringe blood and intervenes hostile to apoptotic phase of develop positive T cells decline sebaceous organ lipid creation [12].

KLF2 assumes a basic part in inflammation through a significant raised articulation levels of IL-1, IL-6, TNFα and MMPs. It is entrenched that the emission of proinflammatory cytokines, for example, IL1, IL8, TNF-α and MMPs adds to the incendiary idea of skin inflammation [1] This suggests the critical function of KLF2 in pathogenesis of skin inflammation.

In this investigation, we found that the mean estimation of KLF2 was lower in provocative skin break out gathering (0.27) than in the non-incendiary skin inflammation gathering (0.95) (P<0.001).Nearly a similar outcome was gotten by Wang et al. who found that ulcerative colitis (UC) patients as an ongoing incendiary sickness communicated lower KLF2 than that of controls, which was more huge in extreme ulcerative colitis patients than gentle cases [13].

As respects Global Acne Severity scale we found that the mean estimation of KLF2 was lower in grade V skin break out cases(0.22), grade IV (0.29) and grade III (0.48) than in non-fiery skin inflammation bunch grade II (0.93) and grade I (0.96).This signifies that KLF2 was most minimal in provocative skin inflammation gathering. Nayak et al. expressed that inadequacy of KLF2 upgrade proinflammatory cytokines articulation [6].

Gao et al. discovered that in osteoarthritis understanding KLF2 mRNA levels steadily diminished as the evaluation expanded from grade 1 to review 4. This may interface the seriousness of the sickness to the degree of KLF2 [14].

As respects to the example of recuperating of skin break out sore, we found that the mean

estimation of KLF 2 was lower in cases mended by scarring (0.23) than in cases mended by post incendiary hyper pigmentation (0.37) (P=0.016) which indicates persistent cycle of aggravation in instances of scarring. Holland et al. discovered that the fiery reaction has been embroiled as a significant part in the improvement of scar [15].

Holy person Jean et al. discovered that nonaPPearance of the advancement of scars is related with low articulation of suPPortive of fiery cytokines as TLR2, IL2, TNFα and MMPs [16].

5.Conclusion

KLF2 could serve as a marker of inflammation and scarring in acne vulgaris.

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