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I-KappaB Expression in Patient with Psoriasis Vulgaris

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Abstract:

The goal of this study is to measure serum level of I Kappa B in patients with psoriasis in comparison with healthy controls. 50 psoriatic patients and 40 age & gender matched apparently healthy controls were included in the study, patients were classified according to Psoriasis Area & Surface Index (PASI) score and serum samples for all participants were taken to measure I Kappa B level for each. The level of serum I Kappa B was found to be significantly lower in the patients (3.96 ±1.96) than in controls (11.02 ±2.22). This difference was of statistical significance (p-value =0.001).

Keywords: Psoriasis, I Kappa B and NF-KB.

1. Introduction:

Psoriasis is considered one of the long-lasting inflammatory disease that involves the innate as well as the adaptive immune compartments (1), characterized by erythematous plaques with thick silvery scales (2). In fact, there are 5 principal types of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic (3).

Psoriasis vulgaris influences the back of the forearms, umbilical region ,shin of tibia, knee , palm ,sole and scalp particularly (4). The pathophysiology of psoriasis is multifaceted and dynamic, comprising a complex interplay between cells of skin and innate& adaptive immune system (5).

All IkB proteins have the capability of binding with high affinity forming stable complexes with dimeric NF-kB proteins, the classical and precursor IkB function primarily as inhibitors by retaining NF-kB in a transcriptionally inactive condition within the cytoplasm. These inhibitors have different binding preferences and specificities for different subunits of NF-kB . These nuclear IkB proteins are accompanied by special NF-kB dimers (6).

Noteworthy, NF-kB is a pivotal inflammatory mediator in psoriasis pathogenesis ; elevated expression of NF-kB has been determined in psoriasis lesions (7). During inflammation, activation of NF-KB results in elevated expression of adhesion molecules vascular cell adhesion molecule (VCAM-1), intracellular adhesion molecule (ICAM-1), and E-selectin whereas its inhibition results in decreased leukocyte adhesion as well as transmigration
(8).

The findings regarding epidermal nuclear positivity of NF- B are correlated with the grade of epidermal hyperplasia and confirm the role of this important family of proteins in psoriasis pathogenesis. In psoriasis, an imbalance between the anti- apoptotic role and the cell cycle inhibitory role of NF- B has been demonstrated . The anti- apoptotic role seems to be dominant that might be responsible for the elevated epidermal thickness cor elating with nuclear NF- B positivity (9), who postulated that NF- B activation might have an essential role in increased keratinocyte survival in addition to epidermal hyperproliferation in psoriasis. Thus, reducing NF- B by therapeutic methods might result in significant decrease in epidermal thickness (8).

2. Patients and Methods:

This was a randomized study performed in Beni-Suef university hospital and Central Elfashn hospital within six months from April to October 2019 involving 90 partner verbal consents were obtained.

2.1 Inclusion criteria:

1-Patients with psoriasis vulgaris regardless of their age and sex.

2-Healthy control group will be age and sex matched with our patients.

5-Exclusion criteria:

1-Patient on phototherapy.

2-Patient suffering from cutaneous tumor.

3-Patients receiving drug that may interfere with level of NF-KB so affect IKB.

4-Patients with other autoimmune diseases.

2.2 All patients were subjected to:

1-Full history, full clinical examination and taking serum sample.

2-Psoriatic patients will be classified according to severity via PASI score.

3- Before the beginning of the study and in accordance with the local regulation followed, the protocol and all considering documents will declare for Ethical and Research approval. Informed consent will be obtained from all patients to participate in this study.

4 - Full informed consent: the purpose of the study was explained for each patient. A written informed consent was taken from each patient. Local research ethics approval was taken before starting data collection. With respect to patients' confidentiality, patients were represented in the study by code numbers. All personal data were concealed. The study protocol conforms to the ethical guidelines of

the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

5- Full history: Including age, gender, occupation, duration of psoriasis, family history and any systemic or local disease were asked for.

6- Full general and dermatological examination at the same time of presentation: all the patients were examined for the degree& severity of psoriasis and for the existence of any skin disease or any general disease. The principal characteristics of the plaque heaviness are redness, thickness and scaling were detected. Each of these parameters was assessed in points from 0 - 4, namely: 0 – absence, 1- mild affection, 2 –moderate affection, 3 –strong severity and 4 –very strong severity. In particular, when it comes to erythema, the degree of redness is assessed as follows: 1 – Light red, 2 – red, but not deep, 3 – very red and 4 – extremely red. While assessing thickness, the points are given depending on the following scoring: 1 – Mild, <0.25mm of plaque thickness, 2 – Moderate, within the limits of 0.5mm, 3 – severe thickness < 1 mm, 4 – for Very Severe character of plaque induration ~1.25mm.

A PASI score was used to measure the severity and extent of psoriasis .It needs a few minutes and experience to calculate it accurately.

Statistical methodology

• Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows;

- Description of quantitative variables as mean, SD and range.
- Description of qualitative variables as number and percentage.
- Unpaired t-test was used to compare quantitative variables, in parametric data (SD < 50 % mean)

• P value > 0.05 insignificant

• P < 0.05 significant

• P < 0.01 highly significant (10).

3. Results:

The current study was conducted at Beni-Suef university hospital and Central Elfashn hospital within six months from April to October 2019. A total of 90 person divided into two groups:

Group 1: Comprising 50 patients having psoriasis vulgaris. Diagnosis will be confirmed based on the typical clinical picture. They will be recruited from outpatient clinic of the dermatology department of Beni-Suef University Hospital.

Group 2: Comprising 40 apparently healthy age- and sex-matched individuals as controls, giving no personal or family history of psoriasis. Control subjects will be recruited from among medical students, health care personnel and patients presenting at the dermatological outpatient clinic with skin tags. They will be selected not to have any

autoimmune illness and on no interfering medications..

Table (1): Gender and age distribution of the studied population; (N= 90):

	Patients with psoriasis vulgaris N= 50	Normal Healthy Controls N= 40	TOTAL	p-value
Gender; N (%)				
Male	34 (68.00	25 (62.5)	59 (65.6)	0.373
Female	16 (32.0)	15 (37.5)	31 (34.4)	
Age; (years)				
Mean ±SD	42.38 ±15.02	44.12 ±14.93	43.15 ±14.9	0.584
Range (Maximum – Minimum)	(75 – 16)	(75 – 16)	(75 – 16)	

(a) Gender (b) Age; (years)

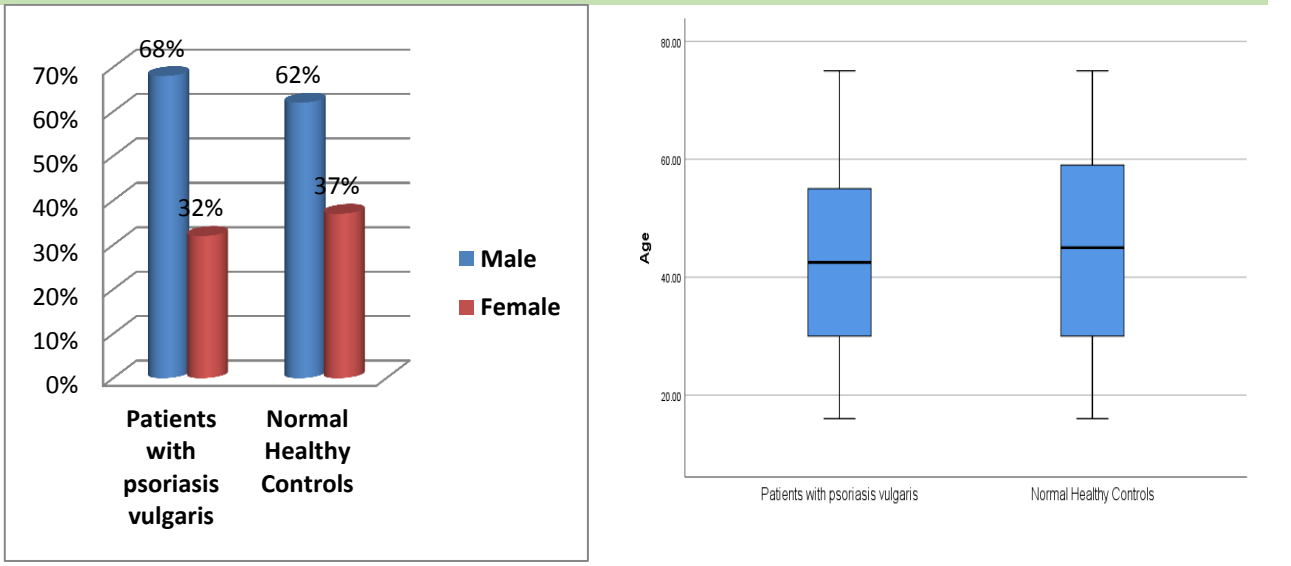

Figure (1): Gender and age distribution of the studied population.

Table (2): Skin types among studied patients with psoriasis vulgaris; (N= 50):

	Frequency	Percent
Skin type III	16	32.0

Skin type IV	20	40.0
Skin type V	14	28.0

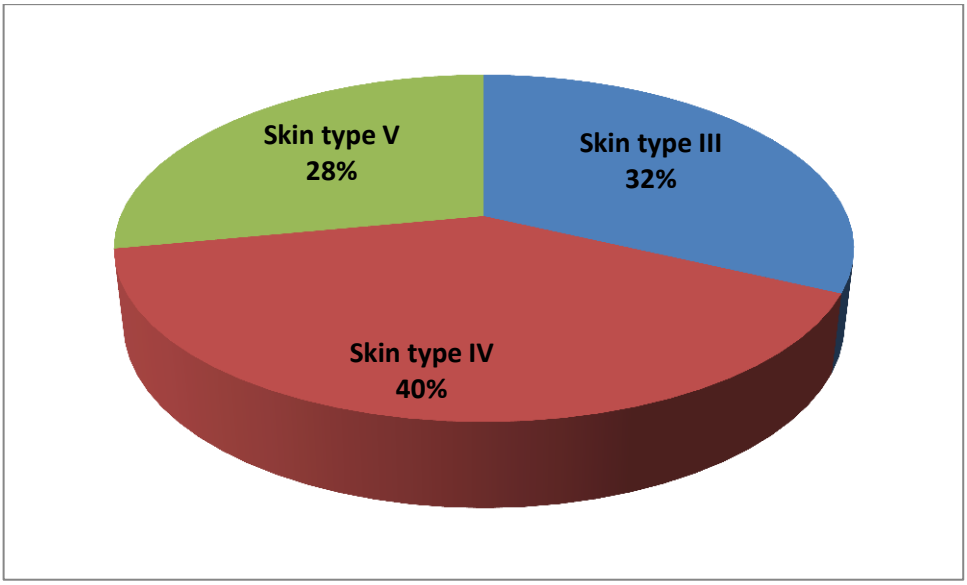

Figure (2): Skin types among studied patients with psoriasis vulgaris.

Table (2) & figure (2) show that examining the skin type among studied population revealed that; the most predominant skin type was type (IV) in 40% of participants, followed by type (III) in 32% and lastly by type (V) in 28% of studied patients with psoriasis vulgaris.

Table (3): Disease Duration and Course among studied patients with psoriasis vulgaris; (N= 50):

	Frequency	Percent
Disease Course		
Progressive	20	40.0
Stationary	30	60.0
Disease Duration; (years)		
Mean ±SD	5.23 ±4.5	
Range (Maximum – Minimum)	(20 – 0.17)	

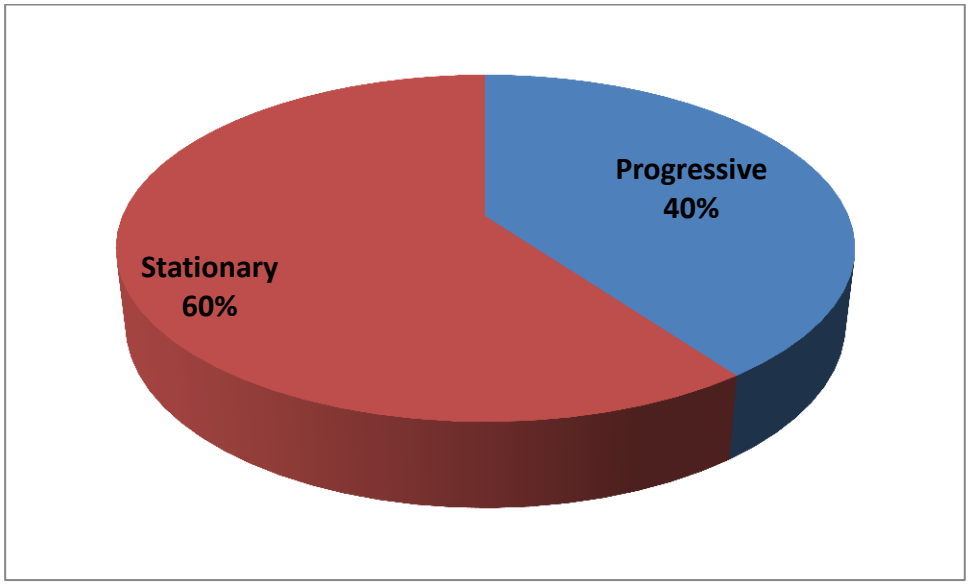

Figure (3): Disease Course among studied patients with psoriasis vulgaris.

Table (3) & figure (3) show that disease duration was ranged from less than one year to (12) years with an average duration of (5.23 ±4.5) years. While the disease course was distributed as; stationary course among (60%) of cases and progressive course among (40%) of them.

Table (4): Treatment modalities among studied patients with psoriasis vulgaris; (N= 50)

	Frequency	Valid Percent
Topical Steroid	27	54.0
Topical Steroid & Methotrexate	1	2.0
Topical Calcineorin inhibitors	7	14.0
Topical Steroid &Salicylic	4	8.0
Topical Steroid & NB-UVB	7	14.0
Topical Steroid & Acitretin	2	4.0
Topical Calcineorin inhibitors & Methotrexate	1	2.0
Topical Steroid & vitD analogues	1	2.0

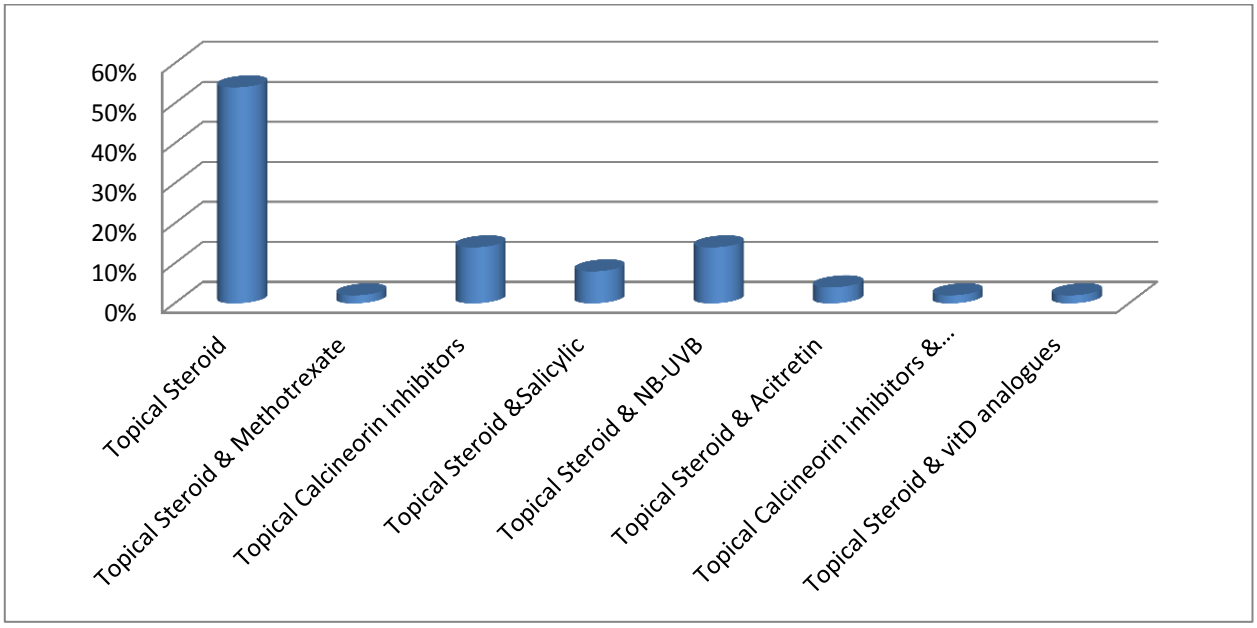

Figure (4): Treatment modalities among studied patients with psoriasis vulgaris.

Regarding history of previous treatment table (4) &figure (4) show that; Topical Steroid was the most prevalent treatment used for management of psoriasis vulgaris among studied cases in the present study with or without other treatments.

Table (5): Comparison of I-Kappa B in studied population; (N= 90):

	Patients with psoriasis vulgaris N= 50	Normal Healthy Controls N= 40	p-value
Mean ±SD	3.96 ±1.96	11.02 ±2.22	**0.001***
Range (Maximum – Minimum)	(10.90 – 2.01)	(16.70 – 8.20)	

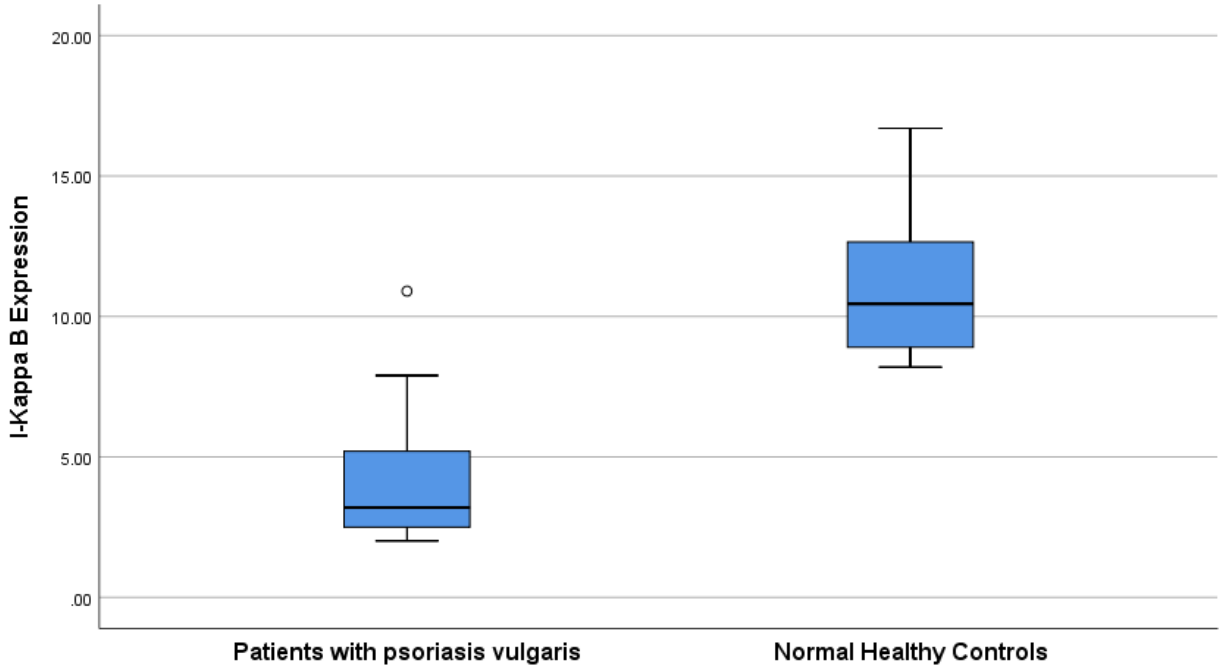

Figure (5): Comparison of I-Kappa B in studied population.

Table (5) &figure (5) show that the expression of I-Kappa B in Patient with Psoriasis Vulgaris was significantly lower as compared with the level among normal healthy control individuals; the serum levels were (3.96 ±1.96 vs. 11.02 ±2.22) in studied Patient with Psoriasis Vulgaris and healthy controls respectively; (p-value =0.001).

Table (6): Relation of Expression of I-Kappa B in Patient with Psoriasis Vulgaris to their gender

	Male N= 34	Female N= 16	p-value
Expression of I-Kappa B			
Mean ±SD	3.88 ±1.7	4.11 ±2.3	0.414
Minimum	2.01	2.07	
Maximum	7.90	10.90	
Range	5.89	8.83	

Table (6) show that there is no detected association between Expression of I-Kappa B in Patient with Psoriasis Vulgaris to their gender; (p-value >0.05).

Table (7): Relation of Expression of I-Kappa B in Patient with Psoriasis Vulgaris to Disease Course

	Stationary N= 30	Progressive N= 20	p-value
Expression of I-Kappa B			
Minimum	3.67 ±2.2	4.14 ±1.7	0.708
Maximum	2.01	2.10	
	10.90	7.90	
Range	8.89	5.80	

Table (7) show that there is no detected association between Expression of I-Kappa B in Patient with Psoriasis Vulgaris to Disease Course; (p-value >0.05).

Table (8): Relation of Expression of I-Kappa B in Patient with Psoriasis Vulgaris to their skin type:

	Skin type (III) N= 16	Skin type (IV) N= 20	Skin type (V) N= 14	p-value
Expression of I-Kappa B				
Mean ±SD	4.31 2.4	3.69 1.6	3.91 1.8	0.655
Minimum	2.07	2.01	2.10	
Maximum	10.90	7.10	7.90	
Range	8.83	5.09	5.80	

Table (8) show that there is no detected association between Expression of I-Kappa B in Patient with Psoriasis Vulgaris to their skin type; (p-value >0.05).

Table (9): Correlation between Expression of I-Kappa B in Patient with Psoriasis Vulgaris and patients' age

	Expression of I-Kappa B in Patient with Psoriasis Vulgaris	
	R	p-value
Patients' Age	0.206	0.150

Statistical analysis was carried out using Spearman's correlation analysis.

r= Spearman's rank correlation coefficient, *p-value ≤0.05 is considered significant.

According to Spearman's rank correlation coefficient analysis table (9) show that there is no detected correlation between expression of I-Kappa-B in patient with psoriasis vulgaris and their age, but value of correlation coefficient (r) and its direction was recorded for screening purposes.

Table (10): Correlation between Expression of I-Kappa B in Patient with Psoriasis Vulgaris and Disease Onset

	Expression of I-Kappa B in Patient with Psoriasis Vulgaris	
	R	p-value
Disease Onset	-0.058	0.689

Statistical analysis was carried out using Spearman's correlation analysis.
r= Spearman's rank correlation coefficient, *p-value ≤0.05 is considered significant.

According to Spearman's rank correlation coefficient analysis table (10) show that there is no detected correlation between expression of I-Kappa-B in patient with psoriasis vulgaris and disease onset, but value of correlation coefficient (r) and its direction was recorded for screening purposes.

Table (11): Correlation between Expression of I-Kappa B in Patient with Psoriasis Vulgaris and Number of plaques

	Expression of I-Kappa B in Patient with Psoriasis Vulgaris	
	R	p-value
Number of plaques	-0.164	0.254

Statistical analysis was carried out using Spearman's correlation analysis.
r= Spearman's rank correlation coefficient, *p-value ≤0.05 is considered significant.

According to Spearman's rank correlation coefficient analysis table (11) show that there is no detected correlation between expression of I-Kappa-B in patient with psoriasis vulgaris and number of plaques, but value of correlation coefficient (r) and its direction was recorded for screening purposes.

4. Discussion:

Psoriasis is one of the long-lasting inflammatory diseases that involves the innate as well as the adaptive immune elements (1), characterized by erythematous plaques with thick silvery scales (2).

In fact, the pathophysiology of psoriasis is multifaceted and dynamic as it involves a complex interplay between different skin cells along with innate and adaptive immune system cells (5).

The classical IκB proteins have the same central ankyrin repeat domain (ARD) composed of 6 ankyrin repeats. The complete length of IKB is composed of 3major regions: N terminal region of ~70 amino acid, an Ankyrin repeat of ~220 amino acid and a C terminal proline-glutamate-serine-theorine rich sequence(PEST) this c terminal extends from residues275-317; one ankyrin repeats stack forming domains which are frequently found in proteins involved in protein:protein interactions (11).

The ARD of classical IκB is surrounded by sequences which are expected to be unstructured. In IκBα, IκBβ, and IκBε, the N-terminal flexible region has 2 conserved Ser residues within the consensus sequence DSGXXS which are determined to be the region in which the IKK2/ β subunit of the IKK complex is phosphorylated. The classical IκB C-terminal site has a structurally flexible area rich in proline, glutamic acid, serine, and threonine amino acids .It is called the PEST domain and is a region commonly present in proteins that has a rapid proteolytic turnover within cells (12).

Noteworthy, IκBα (the best studied IκB protein) isn't inherently thermodynamically stable as regard its folding and, thus, undergoes degradation in cells via a signal-independent mechanism according to its own PEST domain and the 20 S Proteasome; nevertheless, by binding to NF-kB, the IκBα stability will be markedly increased and its degradation will depend on specific phosphorylation-and ubiquitylation-dependent signaling events (12).

The 2 IκB proteins precursors are p105 and p100 that have important affinity to NF-κB , because both of them are responsible for inhibiting nearly 50% of the NF- κB dimers found in the cytoplasm of resting cells. Due to their NF-κB inhibitory activity, they are also referred to as IκBγ and IκBδ, respectively (13).

There are 3 classical IκB proteins: IκBα, IκBβ, and IκBε. Such inhibitory proteins control the NF-κB via 2 pathways: 1)they regulate the nucleocytoplasmic distribution of RelA or c-Rel subunit-containing NF-κB dimers during non-stimulated conditions . 2) the vast majority of NF-κB activity finally result in elevation of IκBα & IκBε expression and these newly formed IκB proteins have the ability to enter the nucleus on their own in order to competitively eliminate NF-κB from κB DNA and return it to the cytoplasm (14).

In the current study the expression of I-Kappa B in patient with psoriasis vulgaris was (3.96 ±1.96) which is significantly lower as compared with the level among normal healthy control individuals (11.02 ±2.22) , This difference was of statistical significance (p-value =0.001).

In our study, that there is no detected association between Expression of I-Kappa B in Patient with Psoriasis Vulgaris to their skin type; (p-value >0.05).

In our study,there is no detected correlation between expression of I-Kappa-B in patient with psoriasis vulgaris and disease onset, but value of correlation coefficient (r) and its direction was recorded for screening purposes.

In our study, there was no detected statistical association between expression of I-Kappa B in Patient with psoriasis vulgaris to their gender, age, skin type, course of the disease, onset, duration, skin type and number of plaques.

The study (15) reported that, several inflammatory factors, including TNFα and IL-17A, are known to play a major role in the pathogenesis of psoriasis, The study (16) also reported that, intracellular signaling pathways and their importance in psoriasis have a great interest, and signaling pathway as the NF-κB pathway have been determined to be changed in psoriatic skin. Here, we identify for the 1st time to our knowledge IκB as a key regulator of NF-KB pathway that is an inhibitor of it and so result in inhibiting TNFα and IL-17A that are essential for psoriasis development.

As IκB proteins were proved to be essential for regulating NF-KB (17), they act as inhibitors for NF-KB by binding to specific NF-κB dimers (6), and NF-KB is a pivotal inflammatory mediator in psoriasis pathogenesis; high expression of NF-κB has been detected in psoriatic lesions (18), that its activation has a key role in increasing KCs survival, hyperproliferation of epidermis, transcription of proinflammatory cytokines, chemokines, adhesion molecules and the release of proinflammatory mediators as IL- 1, - 6, 8, and TNF- α (8).

In addition, it stimulates the release of IL-17 inducing inflammatory response of psoriasis (19), our study revealed that IKB proteins have a role in psoriasis pathogenesis when its level is decreased in serum that leads to the production of NF-KB and its activation and then release of cytokines, chemokines and adhesion molecules that induce the pathogenesis of psoriasis, and that was approved by assessing the serum level of IKB that was decreased in patients suffering psoriasis when compared with which is assessed for the 1st time in psoriasis.

In this context (20), IkBζ was detected as an atypical nuclear IkB protein, that acts as an activator of a selective subset of NF-kB target genes , The mechanisms of this differential gene regulation by IkBζ are still markedly

undetected, but growing evidence denotes that the transcriptional activity of IκBζ is in particular mediated at the level of chromatin remodeling, however in our study, IKB act as an inhibitor of NF-KB by binding to specific NF-kB dimers.

The study (21), reported that IκBζ is an atypical IκB protein it lacks N-terminal signal-dependent phosphorylation regions or C-terminal PEST regions. Moreover, when it is overexpressed in cells they accumulate in the nucleus also they show binding preference toward NF-κB p50& p52 homodimers and that is against our study, the N-terminal flexible region in the classical IKB protiens containing 2 conserved Ser residues within the consensus sequence DSGXXS that are specific areas for phosphorylation by the IKK2/β subunit of the IKK complex . in addition, it also contains C-terminal region that is characterized by flexibility and it is rich in the PEST domain that is a region com frequently found in proteins that has a rapid proteolytic turnover in cells, a, also classical IKB protiens are p105&p100That has high affinity to NF-κB dimers found in the cytoplasm.

The study (22), reported that IL-17 activates NF-κB, via the IKBζ transcriptional regulator, the study (23), also reported that IKBζ was proved to be a key driver in psoriasis through mediating IL-17A–driven influences, but In our study NF -κB induces the production of IL-17 after sequestration of IKB.

The study (24), reported that IκBζ deficiency also conferred resistance against IL-23–induced psoriasis that is in agreement with our study that IL23 has a major role in the pathogenesis of psoriasis and psoriatic arthritis via interaction with IL17 which is stimulated by NF-KB that is activated by phosphorylation of IKB.

A study by (24) demonstrated that the level of IκBζ was elevated in lesional psoriatic skin in comparison with non lesional psoriatic skin from the same patient , suggesting an essential role of IκBζ in the pathogenesis of psoriasis, but in our study IKB was measured in serum and its level is low in psoriatic patients in comparison to controls.

We suppose that IKB has a role in pathogenesis of psoriasis when it decrease NF-KB level increase and then mediators of psoriatic pathway increase, so if IKB proteins were kept in high level in serum that would help in inhibition of psoriatic pathway and treatment of patients with psoriasis, so IKB is considered as a new and important biomarker that play an important role in the pathogenesis of psoriasis and needs closer attention in the study of psoriasis. However, more studies and wider sample groups are needed to document our preliminary findings.

5. Conclusion and Recommendations:

From the current study we coclude the following：

1- Psoriasis is usually a disease of a clinical diagnosis.
2- Pathogenesis of psoriasis is not fully clear and needs further research.
3- I Kappa B is a new and sensitive biomarker that thought to be incriminated in pathogenesis of psoriasis.
4- I Kappa B has a protective role against psoriasis.

From the current study we recommend the following:

1- Further studies about diagnostic value of I Kappa B in psoriasis are needed.
2- Further studies about prognostic value of I Kappa B in psoriasis are important needed.
3- Further studies are needed regarding the use of I Kappa B as a clinical biomarker during management of psoriasis.
4- More studies are still needed in psoriasis to improve the quality of life of the diseased patients.

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