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EXPRESSION OF GLYCOGEN SYNTHASE KINASE 3 BETA IN PATIENT OF PSORIASIS

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Abstract

The objective of the present investigation was to identify a correlation between GSK3β and the pathogenesis of psoriasis using PCR. A Case-Control research was undertaken from February 2019 to February 2020 at the Dermatology outpatient clinic of Beni-Suef University Hospital. This research included 30 patients with persistent plaque psoriasis and 30 age- and sex-matched healthy controls. Skin biopsies were obtained from all participants in the research (psoriasis sufferers and healthy controls) to examine the expression of GSK-3β. The expression of GSK-3β was markedly elevated in psoriasis skin lesions compared to healthy control skin (5.61 vs. 1.03; p-value <0.001). The expression of GSK3β was marginally elevated in male psoriasis patients relative to females, albeit this difference was not statistically significant (p-value = 0.674).There were non-statistically significant association of (GSK-3β) expression with disease onset, disease course and family

history. Patients' age was moderately negative correlated with (GSK-3β) expression; (r= -0.471, p= 0.009). The PASI score was strongly positive correlated with (GSK-3β) expression (r= 0.776, p<0.001). There may be roles of up-regulated (GSK-3β) in lesional skin of psoriasis patients as compared with healthy controls. Nonetheless, an additional gain-of-function or loss-of-function experiment may be beneficial to clarify the involvement of GSK-3β in psoriatic skin lesions

1. Introduction:

Dysregulated interactions among innate immune cells, T cells, and keratinocytes generate psoriasis, an inflammatory skin disorder that affects 2-3% of the world's population and is characterized by aberrant hyperproliferation of keratinocytes [1].

Initially identified as a phosphorylating and inactivating agent of glycogen synthase, GSK-3 is a proline-directed serine-threonine kinase [2]. The amino acid sequences of the two isoforms, beta and alpha (GSK3-α), are quite similar to each other [3] .

GSK3 is a powerful regulator of inflammation because it promotes the production of inflammatory chemicals and cell migration. Inhibiting GSK3 protects animals against inflammatory diseases [4].

The GSK3-β gene encodes the enzyme GSK3β. As belonging to the subfamily of glycogen synthase kinases, this gene codes for a serine-threonine kinase [5]. Apoptotic pathways, inflammation, energy metabolism, mitochondrial dysfunction, endoplasmic reticulum stress, and glucose homeostasis are among routes it is involved in. There is evidence that this gene is associated with both Alzheimer's disease and Parkinson's disease [6].

According to [7], GSK3β is involved in energy metabolism, the proliferation of neurons, and the formation of body patterns. An increased susceptibility to bipolar disorder is associated with the erratic control and expression of GSK3β [8].

Recent confirmation in the settings of immunological response, cell survival, and cancer has shown the regulatory role of GSK-3β on NF-κB and the inflammatory response. Many animal models of inflammatory illnesses have shown considerable anti-inflammatory advantages after inhibiting

GSK-3β activity, which clearly leads to the inhibition of NF-κB activation [9-11].

Cardiovascular disease, inflammation, neurological problems, and cancer are among the ailments linked to GSK-3β [12]. Researchers have shown that lithium promotes the growth of human keratinocytes by inhibiting GSK-3 [13]. The Wnt/GSK-3β/β-catenin signaling pathway, which promotes keratinocyte hyperproliferation, could play a substantial role in how psoriasis develops [14]. The goal of this study was to find out whether GSK3β is associated with the onset of psoriasis.

2. Patients and Methods:

This research was a Case-Control study carried out from February 2019 to February 2020 at the Dermatology outpatient clinic at Beni-Suef University Hospital, including 30 psoriasis patients of both genders, all of whom came to the dermatology department at Beni-Suef University Hospital. The cohort of psoriasis patients included 19 men and 11 females, with ages ranging from 18 to 75 years, and an average age of 46.13±13.8 years. Thirty healthy controls were selected, matching for age and sex to the psoriasis patients.

2.1. Ethical Consideration:

After explaining the study's goals, all participants signed an informed consent form. Database management was confidential. The Beni-Suef University Faculty of Medicine ethics committee approved the project.

Patients and controls were selected according to the following criteria:

2.2. Eligibility Criteria: Individuals must be between the ages of 20 and 50 years, Persons identified with chronic plaque psoriasis. All genders were included. Controls were matched based on age and sex.

2.3. Exclusion Criteria: Individuals aged over 50 or under 20 years, Individuals presenting with alternative types of psoriasis, Individuals diagnosed with skin cancers or other tumors or Individuals suffering from any form of infection.

2.2.

2.4. All participants, including patients and healthy controls, underwent the following procedures:

- Comprehensive history gathering: (age, sex, onset of psoriasis, duration of psoriasis, progression of psoriasis, family history of psoriasis, and triggering factors of psoriasis)
- Clinical evaluation to ascertain type, extent, and locations of psoriasis.
- The PSORIASIS AREA AND SEVERITY INDEX (PASI) was collected from all cases of psoriasis to assess the severity and extent of the condition.

PUNCH BIOPSIES:

- Tissue samples were collected as 4-mm punch biopsies from both affected and unaffected skin regions (matched samples) of individuals diagnosed with psoriasis. Furthermore, biopsies were collected from individuals in the healthy control group. The biopsies were collected from the buttock region that was not exposed to UV light.
- Real-time qPCR amplification and analysis were performed using an Applied Biosystem with software version 3.1 (StepOne™, USA).
- The primer sequence was, GSK-3: **Forward**, 5′-ACAGCAGCGTCAGAT GCTAA-3′, **Reverse**, 5′-GGGACTGTTCAGGTGGAG-3′. β-actin: **Forward**, 5′-GGAGATTACTGCCCTGGCTCCTA-3′, **Reverse** 5′-GACTCATCGTACTCCTGCTTGCTG-3′

Statistical analysis:

Data was analyzed utilizing SPSS 25. Analysis of results involves employing percentage, alongside mean, and standard deviation. The employed analysis was: Chi Square test ($\chi 2$), student t-test, one-way ANOVA and Pearson's correlation analysis. P-values of 0.05 or lower were deemed significant.

3. Results:

As illustrated in (Table-1) the study included 19 male and 11 female patients with psoriasis, with ages ranging from 18 to 75 years, and an average age of 46.13±13.8. Thirty healthy controls were selected, matched for age and sex to the psoriasis cases. The duration of the disease among the psoriasis patients examined ranged from 1 month to 260 months (21 years), with an average duration of 109.90 ± 87.90 months. The majority of the analyzed psoriasis cases exhibited a gradual onset of the disease, with 28 cases representing 93.3%, whereas only 2 cases, or 6.7%, demonstrated a sudden onset of psoriasis. In the analysis of psoriasis cases, it was observed that over half exhibited a Remission & Exacerbation course, accounting for 17 cases (56.7%). Additionally, seven cases demonstrated a progressive course, four cases were classified as stationary, and only two cases showed a regressive course. Notably, the majority of the cases studied did not have a family history of the disease, with 26 cases (86.7%) falling into this category, while only four cases (13.3%) reported a positive family history of psoriasis. The PASI score observed in the studied psoriasis patients ranged from 0.90 to 28.5, with an average PASI score of 8.09 ± 6.3.

TABLE (1): BASELINE AND CLINICAL DATA OF THE STUDIED POPULATION:

		N (%)		
		Psoriasis Patients N= 30	**Healthy Controls N= 30**	**p-value***
Sex	**Male**	19 (63.3)	15 (50.0)	0.435
	Female	11 (36.7)	15 (50.0)	
Age	**Mean ±SD**	46.13 ±13.8	47.70 ±6.6	0.580
Disease Duration	**Mean ±SD**	109.90 ±87.9	NA	
Family History	**Yes**	4 (13.3%)	NA	
PASI Score	**Mean ±SD**	8.09 **±6.3**		
Onset	**Gradual**	28 (93.3%)	NA	
	Sudden	2 (6.7%)		
Disease Course	**Remission & Exacerbation**	17 (56.7%)	NA	
	Progressive	7 (23.3%)		
	Regressive	2 (6.7%)		
	Stationary	4 (13.3%)		

The expression of GSK3β was notably elevated in patients with psoriasis when compared to healthy controls; the average expression values were (5.61 vs. 1.03) for psoriasis cases and healthy controls, respectively, with a statistically significant p-value of < 0.001, as illustrated in Figure-1. The expression of GSK3β was marginally elevated in male psoriasis patients compared to females; however, this difference was not statistically significant (p-value= 0.674). There were non-statistically significant association of (GSK-3β) expression with disease onset, disease course and family history. Patients' Age was moderately negatively significantly correlated with expression of GSK3β in studied psoriasis patients; (r= -0.471, p= 0.009), **(Figure-2).** PASI score was strongly positively significantly correlated with expression of GSK3β in studied psoriasis patients; (r= 0.776, p<0.001), **(Figure-3).**

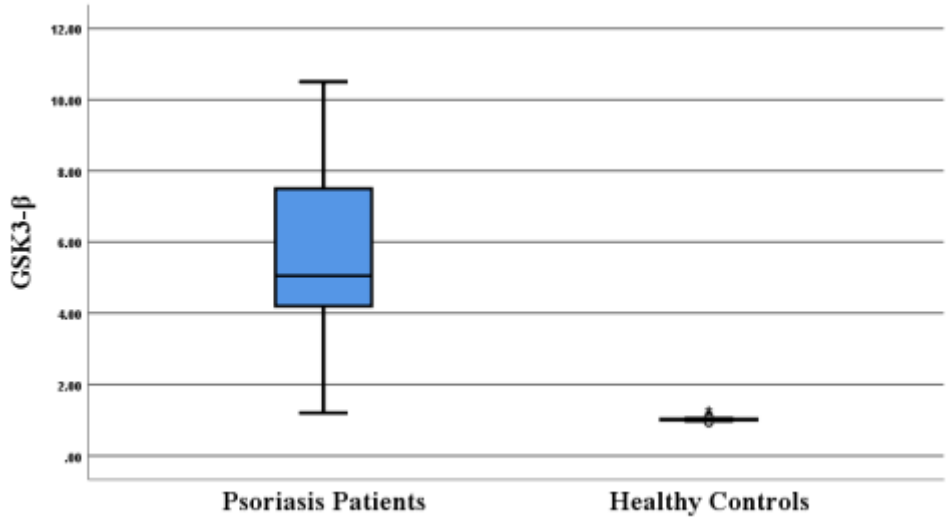

Figure (1): Expression of GSK3β in psoriasis patients as compared with healthy controls.

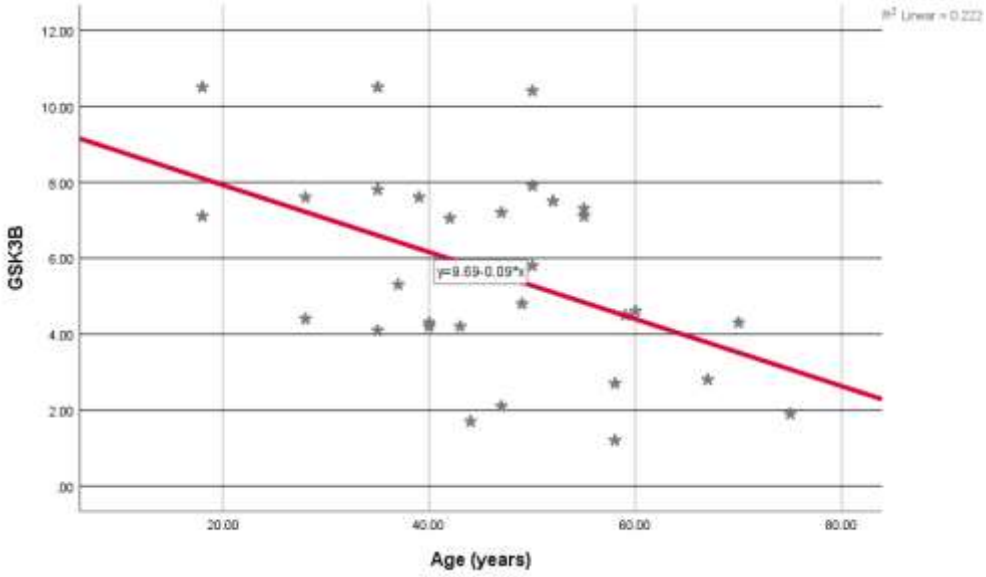

Figure (2): Correlation between Expression of GSK3β and patients' ages

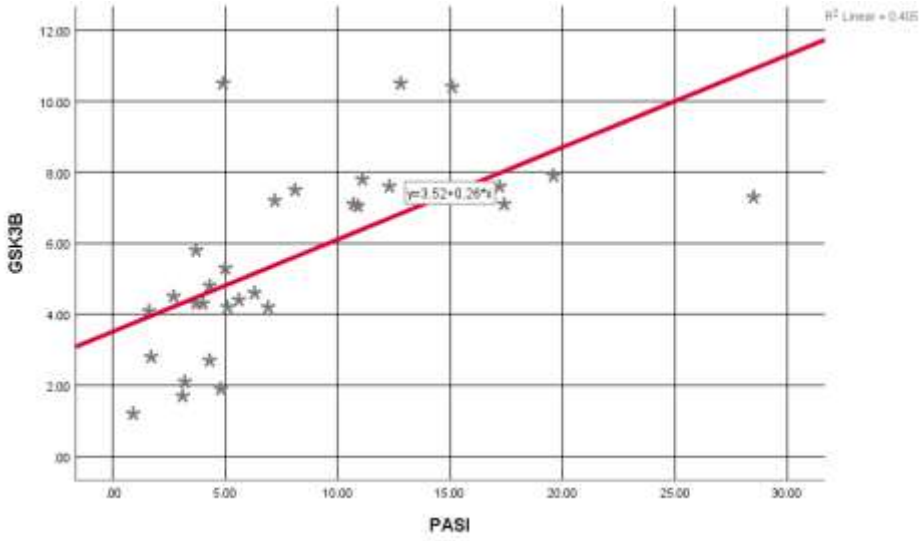

Figure (3): Correlation between Expression of GSK3β and PASI score in studied psoriasis patients

4. Discussion:

An estimated 2-4% of adults suffer from psoriasis, a chronic inflammatory immune-mediated dermatosis [15]. Psoriatic plaques develop as a result of increased keratinocyte proliferation and abnormal keratinocyte differentiation [2]. With the immune system at the center of a complex and poorly understood pathophysiology, there are many unknowns.

The role of the serine-threonine kinase GSK-3 in glycogen metabolism was the first observation of its existence. There are two known isoforms: α and β [16]. There are a number of intracellular signaling pathways that GSK-3 affects, and these pathways control cell survival, proliferation, and differentiation [14].

This study used PCR to find out if there is a connection between GSK-3 β and the way psoriasis becomes worse. Multiple studies have shown that psoriasis affects just as many men as women. In this study, there are 1.7 males for every female participant. There was a 1.9 male-to-female ratio among psoriasis patients aged 60 and above in Côte d'Ivoire, a country with a primarily Black population [17]. In addition to the Mongoloids, males predominate in a number of other groups, such as the Japanese, Chinese, Indians, Taiwanese, and Koreans [18]. On the other hand, studies in the Helsinki area and Turkey found a slightly higher incidence of psoriasis in females [19].

It is known that having a close relative with psoriasis increases the likelihood of developing the condition [20]. A significant number of the psoriasis patients did not have a known family history of the condition. Out of the total number of cases, 26 (86.7%) did not have one, while just 4 (13.3%) did. A research that looked at the clinical and epidemiological features of psoriasis patients at a medical facility in Egypt found a prevalence of 17.5%, which is quite similar to this one [21]. Contrarily, investigations carried out in Italy, Spain, Maghreb, China, and Malaysia indicated family history in 45.9%, 40.7%, 28.6%, 23.1%, and 23.1% of patients, respectively [22]. Cultural and socioeconomic factors that cause people to ignore illness in their own families could explain the observed disparities in prevalence.

The hallmark of psoriasis is the overgrowth of skin cells known as keratinocytes. The impact of GSK-3 β on keratinocyte proliferation in psoriasis remains unclear. The purpose of this study is to look at the potential role of GSK-3 β in psoriasis. According to [23], the expression of GSK-3 β promoted cellular proliferation and survival by facilitating its substrates, which included β-Catenin and cyclin D1. The results of our data analysis showed that GSK3β expression was much higher in psoriasis patients than in healthy controls. The average expression levels were 5.61 in psoriasis cases and 1.03 in healthy controls, with a p-value of less than 0.001. There is little evidence comparing the expression of GSK-3β between healthy skin and psoriatic skin lesions, despite the fact that GSK-3β abnormalities have been linked to several human disorders [24].

The present knowledge of gender variations in this kinase is insufficient; nevertheless, there has been little study on how male and female hormones affect the activity of GSK3β [25]. There was no statistically significant difference between gender and GSK3β (p-value = 0.674), while there was a little increase in GSK3β expression in male psoriasis patients compared to females.

The results show that there is a moderately unfavorable and statistically significant linear relationship (r = -0.471, p = 0.009) between the age of psoriasis patients and the expression of GSK3β. Nevertheless, we did not come across results similar to our present study's when we reviewed previous studies on GSK3β and psoriasis.

The present study found that there is an association between GSK-3β expression and the onset of sickness, the development of the disease, and family history, however it is not statistically significant.

Taking into account both the area covered and plaque morphology, the PASI provides a quantitative measure for evaluating the severity of psoriatic lesions. The PASI scores of the psoriasis patients in this research varied from 0.90 to 28.5, with an average score of 8.09 ± 6.3. The expression of GSK-3β showed a strong positive connection with the PASI score. There has to be more research to confirm or disprove this relationship, but this finding might provide light on how GSK-3β is involved in the pathophysiology of psoriasis and how severe the condition is.

One of the first markers of epidermal keratinocyte differentiation was involucrin, a protein that developed into the crosslinked envelope [26]. In a research that looked at the expression of involucrin in normal and psoriatic skin and how glycogen synthase kinase-3b (GSK-3b) played a role, the authors found that inhibitors of GSK-3b prevented the upregulation of involucrin that IL-17A and IFN-c caused. Both normal keratinocytes and psoriatic keratinocytes support the idea that GSK-3b is involved in the IL-17A and IFN-c driven differentiation process [27].

There is a lack of published research on the expression of GSK-3β in the skin lesions of psoriasis patients, which restricts this study due to substantial gaps in the current body of knowledge.

In comparison to healthy controls, this study sheds light on how up-regulated GSK-3β is involved in the skin lesions of psoriasis sufferers. However, to further understand the function of GSK-3β in skin lesions caused by psoriasis, it could be helpful to do another experiment that involves either gaining or losing function.

5. Conclusion:

Although there are no adequate studies on this research point to prove or deny the role of GSK-3β in psoriasis disease; our current study concluded an up-regulation of (GSK-3β) among lesional skin of psoriasis patients as compared with healthy controls. This result could be a beginning of other research with more different research methods and a larger sample size to explore this difference between GSK-3 β regulation in psoriatic and healthy skin.

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