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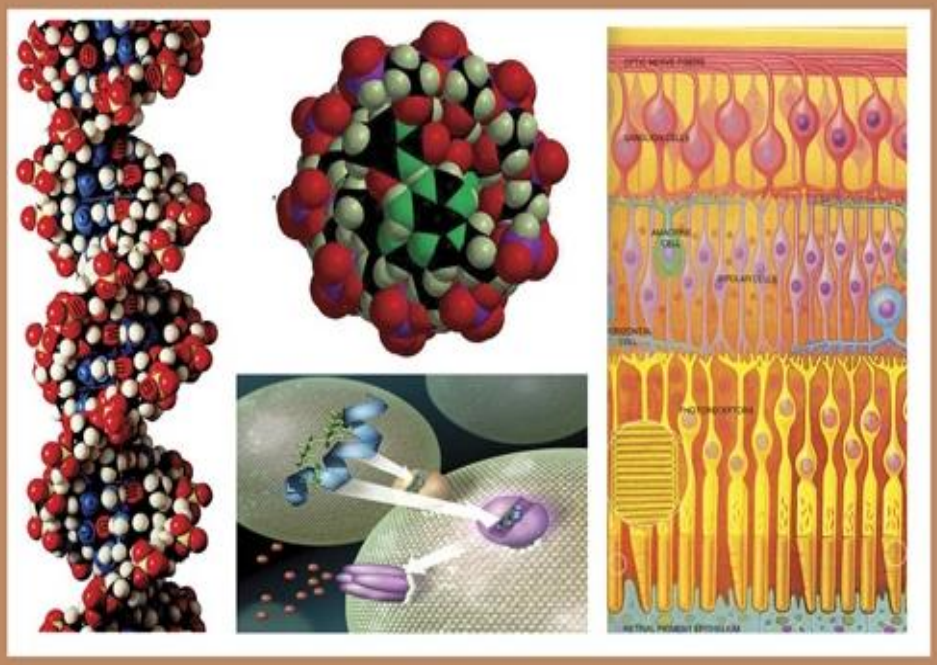

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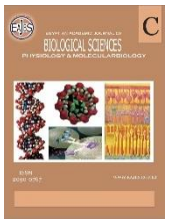

# Estimation of Keratins K5/K14 and miRNA-21 Levels in Keratinocytes of Psoriasis Vulgaris Lesions

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**ABSTRACT**

**Background:** Psoriasis is a common inflammatory skin disease with a global incidence of 1.9%. Its clinical features are red scaly plaques that can affect any part of the body. The aim of this study is to investigate K5 and K14 tissue levels and the possible role of microRNA 21 on their levels in keratinocytes of psoriasis vulgaris patients. **Methods:** The present study included 80 participants divided into 40 psoriasis vulgaris patients and 40 healthy subjects of matched age and gender. All participants were subjected to full history taking and clinical examination. Quantitative real-time PCR was done to estimate the expression level of tissue microRNA 21. As well as estimation of tissue levels of K5 and K14 by ELISA techniques. **Results:** Results revealed that both K14 level and microRNA 21 were significantly increased in Psoriasis patients compared to the healthy group with p-value <0.001. Results showed also a significant positive correlation between K5 and K14 among the control group with p-value <0.001, while a negative correlation was found between K14 and microRNA 21. **Conclusions:** Marked elevation of K14 was found in psoriasis vulgaris epidermis, though K5/K14 is usually paired there was a discrepancy between their levels in the psoriatic lesions, also miRNA-21 was markedly upregulated and was negatively correlated to the high levels of K14. Further studies are needed on wider population for more elucidation of their relationship and their role in the pathogenesis of Psoriasis vulgaris.

## INTRODUCTION

Psoriasis is a common inflammatory skin disease with a global incidence of 1.9% (Lin *et al.*, 2021). Based on the clinical features of skin lesions, psoriasis is classified into four types: plaque psoriasis, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis, of which plaque psoriasis is the most common (Armstrong, 2020). Psoriasis is commonly characterized by well-demarcated raised erythema with thick scales on the surface. Histological manifestations include epidermal hyperproliferation, vascular dilatation in the dermal papilla, and superficial dermal lymphocytic infiltration (Lebwohl, 2018).

The pathogenesis of psoriasis is multifactorial and involves genetic susceptibility, environmental factors, autoantigens and the immune system (Armstrong, 2020). The epidermis plays a critical role in protecting our body against environmental pathogens and stresses by forming different barriers which may be physical or immunological.

This protective role of the skin epidermis is manifested by extensive cytoskeletal architecture. Keratins represent its principal structural protein, contributing to 30–80% of the total protein and forming the major intermediate filament cytoskeleton of the epidermis. This barrier function of the epidermis which is mainly provided by keratinocytes (KC), the predominant cell type in the epidermis, is maintained by a tightly controlled balance between proliferation and differentiation of KC (Zhang, 2018).

There are more than 50 mammalian keratins that have been identified and characterized. Keratins can be sub-classified into two distinct classes: Type I keratins, including K9–K40, are relative acidic (pKi = 4.5–5.5) and small (40–56.5 kDa) whereas type II keratins, including K1– K8 and K71–86), are more basic (pKi = 5.5–7.5) and larger (53–67 kDa) [4]. The active keratin genes are clustered into two dense regions of the chromosome: all type II keratins plus one type I keratin (K18) are located on chromosome 12q, and the remaining type I keratins are all on chromosome 17q. Despite the fact that type I and type II keratins are located at the distinct region of the chromosome, they show beautifully specific patterns of gene expression within adjacent epidermal cell layers and a specific pair of keratins are usually co-expressed as a heterodimer between one acidic (type I) and one basic (type II) keratin. These keratin heterodimers self-assemble into antiparallel, staggered tetramers, yielding intermediate filament through lateral and longitudinal interactions (Zhang, 2018).

Keratin 14 (K14) is a prototypic marker of dividing basal keratinocytes which helps in the maintenance of epidermal cell shape; it also provides resistance to mechanical stress. Interestingly, the K5/K14 pair is expressed in the basal layer of the epidermis, which contains epidermal stem cells and transient amplifying (TA) cells (Alam *et al.,* 2018).

The expression of the keratin 5 (K5) type I–keratin 14 (K14) type II "pair" is specific for the basal cells of squamous stratified epithelium. K5/K14 expression can also persist in suprabasal skin KCs before their entry into differentiation (Evtushenko *et al.,* 2021).

Ultrastructurally, K5/K14 keratin filaments are bundled as tonofilaments and attached to desmosomes and hemidesmosomes. The functional importance of K5 and K14 for the physical stability of the epidermis has become clear by recognizing that dominant-negative mutations of the K5 or the K14 gene cause the hereditary blistering skin disease epidermolysis bullosa simplex. The presence of mutated K5 or K14 results in increased fragility of the basal keratinocytes so that even mild physical trauma leads to intraepidermal cytolysis of basal cells and the formation of fluid-filled blisters (Nejad *et al.,* 2018).

Cells expressing mutated K14 are more liable to stress damage and apoptosis resistance. Thus, mutation of K14 in psoriatic skin might lead to "unnatural" keratin pair, this drastically alters the assembly of network filament as well as the mechanical support in epidermal skin and also increase the degradation of keratin filaments by various stressors leading to acanthosis in psoriasis (Elango *et al.,* 2018).

MicroRNAs are a major class of non-coding RNAs, it is a family of small regulatory RNAs. A large fraction of these transcribed RNAs are not translated into proteins but exhibit regulatory functions that increasingly are recognized as critical factors in development and homeostasis. (Mouillet *et al.,* 2015).

MicroRNAs have been involved in the modulation of both the innate immune response and the adaptive immune response, as well as in a wide range of diseases, including cancers, immunological diseases and several skin diseases. Furthermore, since the discovery of miRNAs, intensive research has not only provided us with new insights into gene regulation, also provided new

directions for future diagnostics and therapy (Nejad *et al.*, 2018).

The human microRNA-21 gene is located on the plus strand of chromosome 17q23.2 (55273409–55273480) within a coding gene TMEM49 (also called vacuole membrane protein). Despite being located in intronic regions of a coding gene in the direction of transcription, it has its own promoter regions and forms a ~3433-nt long primary transcript of miR-21 (known as pri-miR-21) which is independently transcribed. The stem-loop precursor of miR-21(pre-miR-21) resides between nucleotides 2445 and 2516 of pri-miR-21 (Krzywińska *et al.*, 2020).

MicroRNAs-21, maintain skin inflammation and epidermal proliferation in psoriasis patients, it is overexpressed in psoriasis; miR-21 was found in psoriatic skin lesions, psoriatic epidermal cells, dermal T cells and blood samples, and it has a major role in *psoriasis* (Timis and Orasan, 2018)**.**

## MATERIALS AND METHODS

**Ethical Approval:**

The current study was endorsed by the medical ethical committee of Kaser Al-Ainy hospitals. Informed written consent was signed by each patient before enrolment in this study

**Design and Participants:**

A cross-sectional study was conducted in the Molecular Biology Unit of the Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Cairo University. Participants were recruited from the outpatient Dermatology clinic, at Cairo University hospitals. This study included 80 participants divided into 2 groups: case group enrolled 40 psoriasis vulgaris patients (with no history of other dermatological diseases or receiving any treatments). And, control group enrolled 40 healthy subjects of matching age and gender (All recruits were above 18 years with no history of chronic dermatological disease). All patients were recruited in the period between September 2020 till October 2021, Patients were screened for eligibility to participate in this study.

**Skin Biopsy:**

Two mm biopsies were taken under local anesthesia (Lidocaine®) from the psoriatic lesions and excess skin after major operations or minor surgeries in controls. For each subject, one tissue biopsy was added to an eppendorf with 3 ml phosphate buffer saline (PBS) for immunoassay and the other was added to an eppendorf with 700 µl lysis buffer for molecular biology assessment. Eppendorfs were stored at -80$^{o}$C until the time of analysis.

**Laboratory Methods:**

**1. Assessment of K4/15 Using ELISA:**

Tissue levels of human cytokeratin 5 and, cytokeratin 14 were assayed by commercially available ELISA kits supplied by (SUNLONG BIOTECH Co., Ltd., China).

After homogenization and centrifugation of skin biopsies in 300 µl PBS, supernatants were added to the microtiter plates percolated with an antibody specific to the assayed keratin

After adding conjugated antibody, chromogenic substrate solution and, washing steps done according to the manufacturer's instructions, a color change was obtained and detected spectrophotometrically at wavelength 450 nm. A curve plotted between absorbance and concentration levels was created by graph pad prism 9 to obtain the final results Figure 1

.


**Fig. 1:** Human cytokeratin 5 and, cytokeratin 14 calibration curves

**2. Assessment of miRNA-21 using Real-Time PCR:**

**2.1. RNA Extraction:**

Total RNA with preserved small-RNAs was extracted by miRNeasy Mini kit (50) (Qiagen, Germany), first tissue samples in 700 µl QIAzol lysis reagent were homogenized by a grinder, the homogenate was done at room temperature (15–25°C) for 5 min. 140µL chloroform was added to each sample followed by another incubation for 3 minutes and centrifugation for 15 min at 12,000 xg. The upper aqueous phase was transferred to a new tube with 1.5 volume of 100% ethanol added. 700 µl of this mixture were added into Mini column in a 2 ml collection tube, centrifuged at ≥8000x g for 15s at room temperature. After discarding the flow-through, the step was repeated twice; first after adding 700 µL of buffer RW, second after adding 500 µl Buffer RPE. Finally, 50 µl RNase-free water was directly pipetted onto the Mini column membrane, centrifuged for 1 min at ≥8000 xg for elution. Extracted RNA was then stored at –80°C until use.

**2.2. Reverse transcription and Quantitative real-time PCR (qRT-PCR).**

Reverse transcription from micro-RNA into complementary DNAs (cDNAs) was carried out on total microRNA in a volume of 20 ul RT reaction using the (TransScript® miRNA First-Strand cDNA Synthesis SuperMix kit Beijing, China). The mix was incubated at 37 °C for 60 minutes followed by 5 minutes at 85°C to terminate the reaction. Real-time qPCR amplification and analysis were performed using (SYBR Green PCR kit PerfectStart™ Green qPCR SuperMix Beijing, China). A 20 µl mix of Taq qPCR Green Master Mix, forward Primer: CAGATCAGCCGCTGCACA, reverse primer: TGCCCACCGCACAC, template DNA and nuclease-free water was prepared then florescence was detected using a thermal cycler (Step One Applied Biosystem, Foster City, USA).

U6 was used as a reference gene with forward primer: CGCTTCGGCAGCACATATAC, reverse primer: AAAATATGGAACGCTTCACGA. The expression levels of microRNA were evaluated using the Δ Ct method. Relative expression (RQ) was calculated using the $2^{-\Delta\Delta Ct}$ method, first: Δ Ct = Ct assessed gene – Ct reference gene, then: Δ Δ Ct = Δ Ct sample – Ct internal control gene, and finally: RQ = 2 – (Δ Δ Ct).

**2.3. Statistical Analysis:**

Data were coded and entered using the statistical package SPSS version 22 $Chi^2$ test was used when comparing categorical data. Numerical data were summarized using mean and standard deviation. Correlations between quantitative variables were done using Pearson and Spearman correlation coefficients (Chan., 2003).

## RESULTS

There were eighty subjects enrolled in this study, 40 subjects in the control group with mean age (37.3 ±13.6), with 20 (50%) males and 20 (50%) females, while in the 40 psoriasis vulgaris patients' group with mean age (41.1 ±17.6),15 (35%) males and 26 (65%) females. the mean duration of Psoriasis is 129.45±123.3 with a range (1-480) month. The mean PASI score is 11.96± 3.19 with a range (7.3-20.3) Results showed

that there was no statistical significance between the two groups with respect to age (p=0.28) and gender (p = 0.17). (Table 1).

As regards tissue levels of human cytokeratin 5, there is no significant difference in the tissue level of Keratin 5 in Psoriasis patients and healthy subjects with p value=0.13. Figure (2), while there was a significant increase in tissue levels of Keratin-14 in Psoriasis patients compared to control with p value<0.001. Figure (3).

A Significant Positive correlation was found between K5 and K14 (r=0.39, p value =0.002). Figure (4).

Positive correlation was found between:

- K5 and age (r=0.27, p value 0.03). Figure (5).
- K14 and age **(r**=0.12, p value 0.37). Figure (6).

As regards miRNA-21 expression our results show a significant increase in miRNA 21 expression in Psoriasis patients compared to control with p value<0.001. Figure (7).

A significant negative correlation was found between miRNA-21 and K14 among the case group (r=-0. 4, p value =0.012). Figure (8).

**Table 1:** Demographic data among the studied groups

| Variable | Healthy skin subjects | psoriasis vulgaris patients | P-value |
|---|---|---|---|
| **Age (years)** | 37.3 ±13.6 | 41.1 ±17.6 | 0.28 |
| **Sex**<br>**Male**<br>**Female** | <br>20(50%)<br>20(50%) | <br>14(35%)<br>26(65%) | <br><br>0.17 |

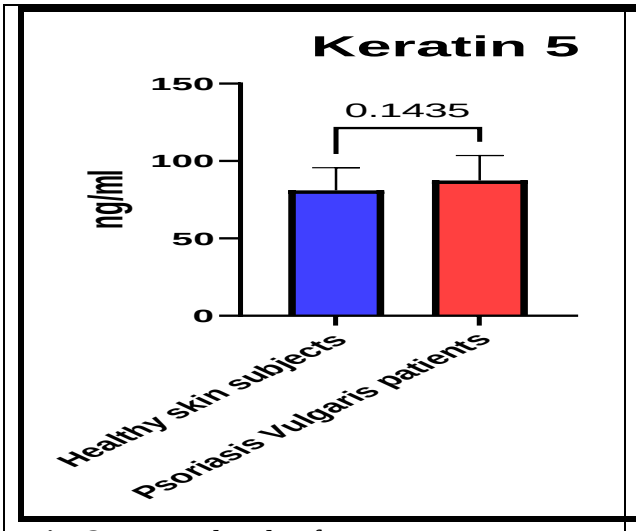


**Fig. 2:** Tissue levels of Keratin-5 among different studied groups.

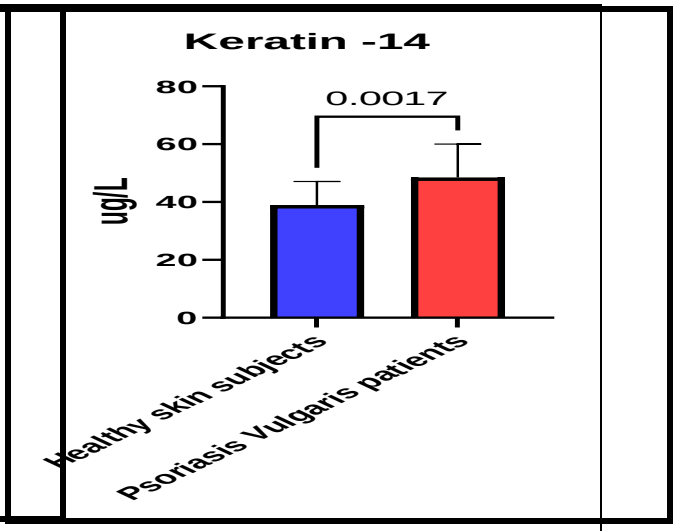


**Fig. 3:** Tissue levels of Keratin-14 among different studied groups**.**

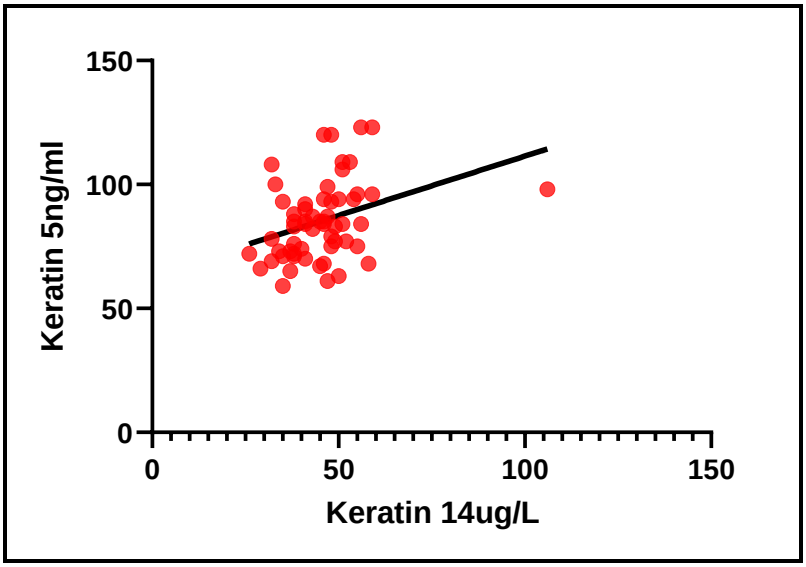


**Fig. 4:** Correlation between K5 and K14

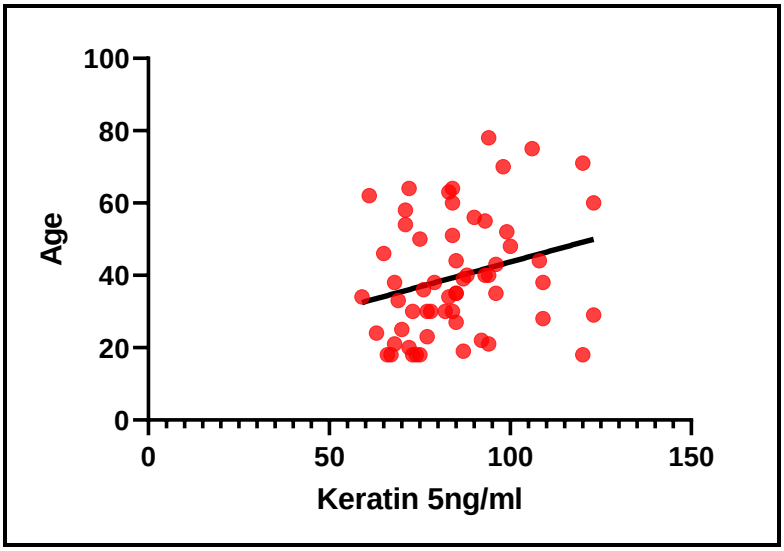


**Fig. 5:** Correlation between K5 and age

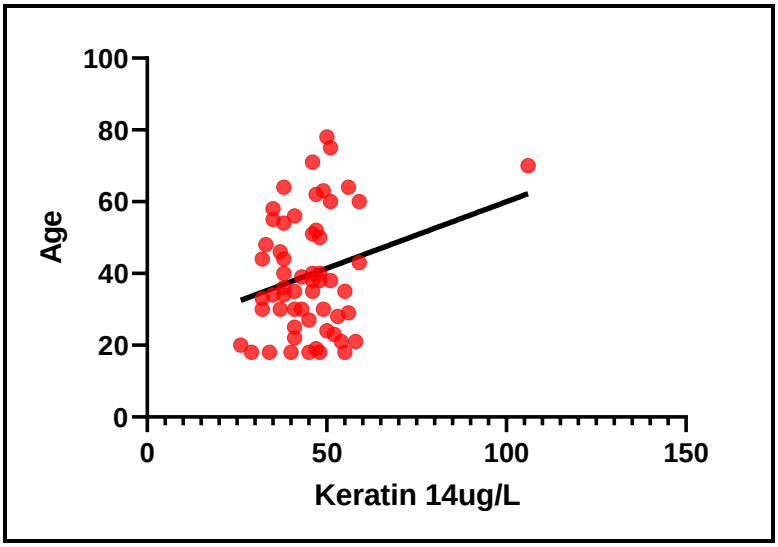


**Fig. 6:** Correlation between K14 and age

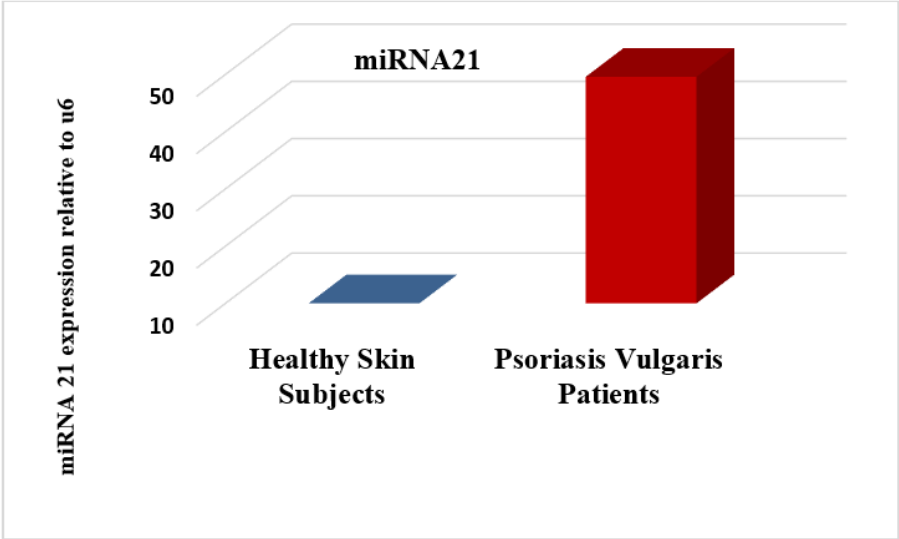


**Fig.7:** miRNA 21 expression among different studied groups.

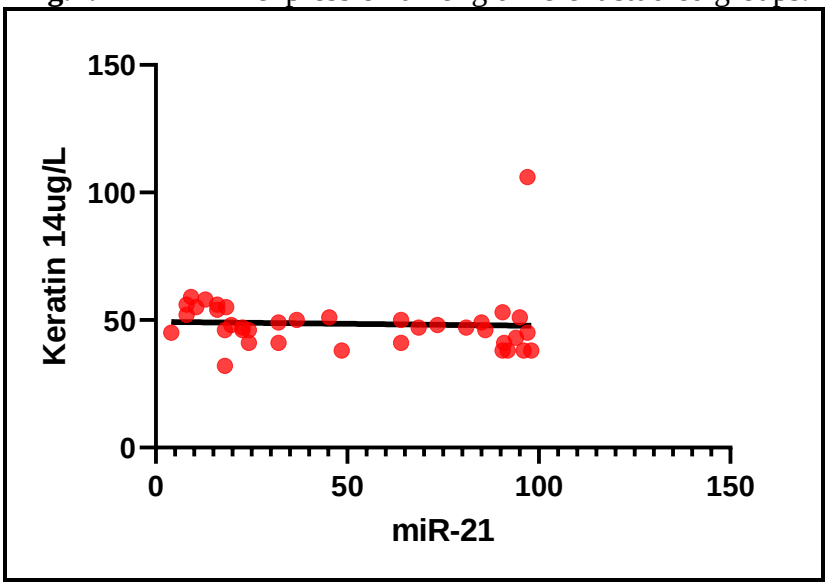


**Fig. 8:** Correlation between miRNA 21 and K14 among case group.

## DISCUSSION

Psoriasis is a common inflammatory skin disease that affects near about 2% of the population in Western countries (Boehncke, 2018). The principal pathogenetic mechanisms underlying psoriasis, including, inflammation, hyperproliferation, and angioneogenesis. Psoriasis is considered an immune-mediated disease, exhibiting an intense cross-talk between components of the innate and the adaptive immune system, which then trigger the epidermal changes (Capon *et al.*, 2012).

The protective role of the skin epidermis is manifested by extensive cytoskeletal architecture, in which keratins represent its principal structural protein (Zhang, 2018). Cytokeratins help cells to endure mechanical stress. The expression of these cytokeratins in epithelial cells is largely set to specific organs or tissues. They are therefore used clinically to identify the cell origin of various human tumors (Kumar and Jagannathan, 2018).

Cytokeratins are encoded by a family of 30 genes. Among them, 20 are epithelial genes and 10 are specific to trichocytes. Based on the remarkable preservation of protein chain structures and keratin genes, it has been suggested that the primary gene was assembled from smaller units encoding multiple heptad repetitions (28 residues or 84

base pairs) separated by intermediate introns (Moll *et al.,* 2008).

Keratin gene expression is developmentally regulated and is not universally expressed during embryonic development; rather, different keratin genes are expressed during different stages of epithelial cell development during embryogenesis (Kumar and Jagannathan, 2018).

The term miRNA was introduced in 2000 when the first human miRNA was discovered (Pasquinelli *et al.,* 2000). Since their discovery, they have received considerable attention in basic research and much progress has been made in elucidating miRNA expression patterns and functions. Currently, 2588 mature miRNAs in humans have been registered in the miRBase database (Panwar *et al.,* 2017).

Waheed and Zeng, estimated that more than 60% of all human protein-coding genes are regulated by miRNAs, making them one of the most abundant classes of gene-regulatory molecules (Waheed and Zeng, 2020).

In our study tissue levels of K5/K14 and miRNA 21 expression were investigated to detect their role in the pathogenesis of psoriasis vulgaris, to clarify this role 80 subjects of matched age and sex were included from the dermatology department, Faculty of Medicine, Cairo University. The subjects were divided into 2 groups: control group consisted of 40 apparently healthy volunteers as healthy skin subjects and the patients' group consisted of 40 psoriasis vulgaris patients.

In this work, the mean duration of psoriasis was 129.45±123.3 months ranging between 1 and 480 months. The mean PASI score is 11.96± 3.19 ranging between 7.3 and 20.3. Also, Elango *et al.,* 2018 study included 96 patients with psoriasis vulgaris with a mean age of $37.97 \pm 14.03$ years ranging from 16 to 71 years. Forty-eight patients with mild psoriasis had a PASI score of $4.06 \pm 2.46$, and the remaining 48 patients with moderate psoriasis had a PASI score of $17.34 \pm 5.64$.

In the current study, there is a significant increase in the tissue level of K14 among psoriasis patients compared to control ($p<0.001$*). This has coincided with Elango *et al.,* 2018 study that showed increased K14 expression at protein and mRNA levels in mild psoriatic skin biopsies compared to non-lesional skin biopsies; in contrast to this, moderate lesional biopsy showed decreased expression of K14 and K10.

Our study showed there is a significant positive correlation between K5 and K14 ($p<0.001$*) This is agreed with Alam *et al.,* 2018 study that reported that the K5/K14 pair is expressed in the basal layer of the epidermis, the same study reported that, K5 and K14 are expressed in the mitotically active basal layer of stratified epithelia. When these cells move upward and differentiate, K5/K14 expression is decreased and K1/K10 expression is induced in the keratinizing layer of stratified epithelia (e.g., epidermis). This is accompanied by an inhibition of cell cycle progression and proliferation.

In agreement Zhang, 2018 reported that type II keratin K5 and type I keratin K14 form the primary keratin pair of the keratinocytes of stratified squamous epithelia, including the epidermis as well as mucosal nonkeratinizing stratified squamous epithelia. They are strongly expressed in the undifferentiated basal cell layer containing the stem cells and are downregulated in the differentiating suprabasal cell layers where K5 and K14 are uniformly expressed throughout all layers.

This is agreed with Evtushenko *et al.*, 2021 who reported that K5 is a marker of mitotically active and regenerative progenitor cells. This makes the K5/K14 complex an important participant in epithelial organ morphogenesis and regeneration. For the same reasons, K5/K14 are markers of oncotransformation and are used to detect lymph node micrometastases. K14-deficient cells demonstrated a reduction in cell proliferation, decrease in phospho-Akt levels, activation of the Notch1 cascade, and increase in the levels of involucrin and K1,

which are known to be markers of KC differentiation.

Elango *et al.,* 2018 also found that, in psoriasis, the expression levels of K5 and K14 in the basal cell layer are altered in the psoriatic epidermis. The hyperproliferation in psoriasis seemed to result from an increase in the number of transit-amplifying cells, following depletion of the stem cell compartment.

Moll *et al.,* 2008 reported that SCC is characterized by extensive expression of K5/K14 through the epidermis and the expression of hyperproliferative keratin K6, K16 and K17, which are not only upregulated in inflammatory skin but often upregulated in many tumors originating in stratified and pseudostratified epithelia.

Our study found a positive correlation between both of K5 and K14 and age, this is not coinciding with Engelke *et al.,* 1997 who reported that: In aged/normal compared with young/normal skin there was a significant decrease in proliferation. However, epidermal proliferation was the same in aged/dry skin as in young/normal skin. For epidermal differentiation, an age-independent decrease of keratins K1 and K10 and an associated increase in the basal keratins K5 and K14 were detected in dry skin. Also, Oender *et al.,* 2008 reported that the mRNA levels of the genes for K1, K3, K4, K9, K13, K15, K18, K19 and K20 are downregulated in aged skin, K5 and K14 are unchanged.

According to the current study, the expression of miRNA 21 was significantly higher among psoriasis patients compared to control ($p<0.001$*). This is coinciding with *Guinea*-Viniegra *et al.***,** *2014* who reported that Over-expression of miR-21 has been demonstrated in skin abrasions of patients with psoriasis and in association with down-regulation of TIMP-3 expression and stimulation of TACE/ADAM17.

In concordance, Timis & Orasan, 2018 study indicated that microRNAs regulate the expression of their target genes at a post-transcriptional level. Dysregulation in the expression of these transcripts contributes to the pathogenesis of psoriasis.

Another study by Yan *et al., 2019* reported that ncRNAs and microRNAs have functional interactions that are involved in the regulation of immune response and the pathophysiology of inflammatory disorders such as psoriasis. Massive dysregulation of ncRNAs in psoriasis might participate in the pathogenesis of psoriasis.

In agreement, Morlang *et al.,* 2021 reported that miRNAs-21 are expressed not only by keratinocytes, but also by infiltrating immune cells, and hence it is not surprising that an upregulation can be found in other allergic conditions or T-cell-mediated skin diseases such as contact dermatitis, asthma, eosinophilic oesophagitis and psoriasis.

In concordance, Li *et al., 2017* reported that there is increased expression and upregulation of microRNA-21 in fibrotic skin diseases.

Our study found a negative correlation between K14 and microRNA-21 among case group ($p<0.0001$*), this is coinciding with Ahmed *et al.,* 2011 who reported that increased levels of miR-21 were observed in transgenic mice overexpressing the BMP antagonist noggin under control of the K14 promoter (K14-noggin).

**Conclusion**

In conclusion, our study showed marked elevation of K14 in psoriasis vulgaris epidermis, which goes with respect to the undifferentiated status of the disease, though K5/K14 is usually paired there was a discrepancy between their levels in the psoriatic lesions, also miRNA-21 was markedly unregulated and was negatively correlated to the high levels of K14. Further studies are needed on the wider population for more elucidation of their relationship and their role in the pathogenesis of Psoriasis vulgaris.

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## ARABIC SUMMARY

**تقدير مستويات الكيراتين K5 / K14 وmiRNA-21 في الخلايا الكيراتينية المصابه بمرض الصدفية الشائع**

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**الخلفية:** الصدفية مرض جلدي التهابي شائع تبلغ نسبة الإصابة به 1.9٪، وتتمثل سماته السريرية في لويحات متقشرة حمراء يمكن أن تصيب أي جزء من الجسم. الهدف من هذه الدراسة هو فحص مستويات K5 وK14 في الانسجة والدور المحتمل لـ microRNA 21 على مستوياتها في الخلايا الكيراتينية لمرضى الصدفية الشائع.

**طرق البحث:** اشتملت الدراسة الحالية على 80 مشاركًا مقسمين إلى 40 مريضًا بالصدفية و40 شخصًا يتمتعون بصحة جيدة من نفس العمر والجنس. خضع جميع المشاركين لأخذ التاريخ الكامل والفحص السريري. تم إجراء تفاعل البوليميراز المتسلسل في الوقت الحقيقي الكمي لتقدير مستوى التعبير عن الرنا الميكروي للأنسجة 21. بالإضافة إلى تقدير مستويات الأنسجة لـ K5 وK14 بواسطة تقنياتELISA

**النتائج:** أظهرت النتائج أن كلا من مستوى K 14 وmicroRNA 21 قد زاد في مرضى الصدفية مقارنة بالمجموعة السليمة ذات القيمة الاحتمالية <0.001. كما أظهرت النتائج وجود علاقة ارتباط موجبة بين K5 وK14 بين المجموعة السليمة مع قيمة p <0.001، بينما وجد ارتباط سلبي بين K14 و microRNA 21.

**الاستنتاجات**: تم العثور على ارتفاع ملحوظ لـ K14 في البشرة الصدفية الشائع، على الرغم من أن هناك عادة اقتران بين K5 / K14 فقدوجد تباين بين مستوياتهما في آفات الصدفية، كما أن هناك ارتفاع في مستوي miRNA-21 بشكل ملحوظ وكان مرتبطًا سلبًا بالمستويات العالية من K14. هناك حاجة إلى مزيد من الدراسات على عدد أكبر من السكان لمزيد من توضيح علاقتهم ودورهم في التسبب في مرض الصدفية