

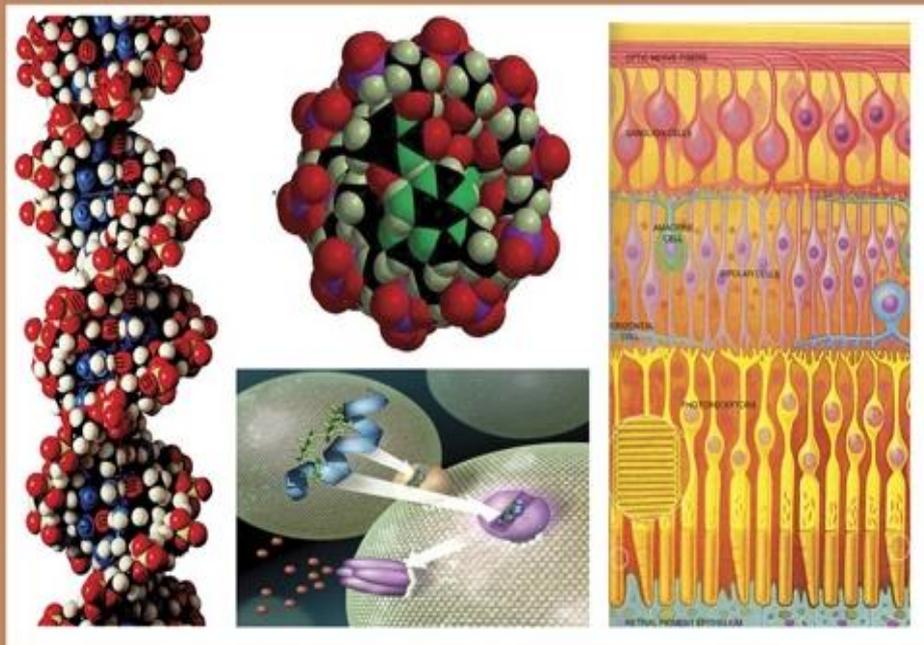


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Level of Autophagy in Lichen Planus: Role of Endoplasmic Reticulum Stress Proteins

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ABSTRACT

Lichen Planus (LP) is a common T cell-mediated chronic inflammatory disease affecting skin & or mucous membranes. Also, T cell-induced autophagy is involved in the immunopathogenesis of the oral type of lichen planus (OLP). Beclin-1 is an autophagy marker with a critical role in the autophagic process. Heat shock proteins (HSP) synthesis increases in response to many stressors being the molecular chaperones. HSP has an important role in the Endoplasmic reticulum stress (ER stress) process. HSPs are assumed to be involved in the initiation and probably continuation of lichen planus through the autoimmune lymphocytic response. GRP78 (Glucose-regulated protein 78) is one of the HSPs that may play a substantial role in LP. ATF6 (activated transcription factor6) is one of ER stress pathway sensors that may link ER stress and autophagy. The study was conducted on 40 lichen planus patients and 20 healthy control subjects. GRP78, ATF6 and Beclin-1 gene expressions were estimated by real-time PCR. Patients with oral and cutaneous lichen planus showed a significant increase in GRP78, ATF6 and Beclin-1 compared to the normal control group. Conclusion; the results conduct an increase in autophagy and endoplasmic reticulum stress markers with lichen planus which may represent an inductive or protective mechanism for lichen planus.

INTRODUCTION

Lichen planus (LP) is an idiopathic chronic inflammatory disease affecting the skin, mucous membrane & skin appendages. On the skin, lichen planus usually demonstrates purplish, often itchy, flat-topped bumps while in the mouth, vagina and other areas covered by a mucous membrane, lichen planus may produce lacy white patches; red, swollen tissues, or sometimes painful open sores (*Bradford and Fischer, 2013*). Oral lichen Planus (OLP) is an ongoing (chronic) inflammation with no cure that has a significant impact on patients' quality of life. One of the most serious complications of OLP is malignant transformation into squamous cell carcinoma (SCC) (*Tampa et al., 2018*).

Autophagy (self-eating) sequesters, degrades and recycles cellular material. Autophagy is necessary and beneficial to the cell and organism because it prevents the build-up of toxic protein aggregates, removes damaged organelles, and provides the cell and organism with bioenergetic substrates needed to survive (*Doherty & Baehrecke, 2018*). Autophagy is involved in various innate and adaptive immune processes, including pathogen recognition and destruction, antigen processing for MHC presentation, lymphocyte development and function, and inflammatory regulation (*Levine et al., 2011*).

Mammalian Beclin 1, the ortholog of yeast autophagy-related gene 6 (Atg6), is involved in the regulation of the autophagic process at a critical step, namely, autophagosome formation (*Maejima et al., 2016*). In recent years, the evaluation of autophagy gains a great interest. It has been found that autophagy-related genes dysregulation is associated with an increase the susceptibility to multiple diseases, including inflammation, autoimmune disorders, and cancer (*Cheong, 2015*).

There is a great suggestion between the different clusters of autophagy-related genes expression in OLP and differences in T cell autophagic activity that may be associated with the different clinical forms (*Tao et al., 2007*). ATG9B (autophagy-related 9B) is one of the autophagy markers that its expression in T cells of non-erosive OLP is decreased. This decrease may represent compromised autophagy, which could lead to less apoptosis of keratinocytes. Thus, different ATG9B expressions in T cells of OLP may contribute to the epithelial damage with different clinical presentations (*Tan et al., 2016*).

Under various physiological and pathological stimuli, ER homeostasis is disrupted. These stimuli include toxins, viral infections, inflammatory cytokines and mutant protein expression leading to endoplasmic reticulum stress (ER stress) with an accumulation of misfolded and unfolded proteins. In response to ER stress, a complex signaling network referred to as the Unfolded Protein Response (UPR) is activated to reduce ER stress and restore homeostasis. However, if the UPR fails to renormalize the ER homeostasis, ER UPR provides the cell machinery with situational awareness of the peptide-folding environment via three protein sensors embedded in the ER membrane; activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and PKR-like Pancreatic ER kinase (PERK). Binding immunoglobulin protein (BiP) (also known as GRP78 and is a member of heat shock

proteins being HSPA5) transiently binds to the luminal domain of each receptor (*Lewy et al., 2017*). ER GRP78 can migrate out of ER into the nucleus (intracellular) where it has a vital role in protein folding as a cell chaperone in the ER and is anti-apoptotic protecting cells under stress (*Panayi and Corrigall, 2014*) or to the cell surface (extracellular) where GRP78 has powerful anti-inflammatory and immunomodulatory properties (*Shields et al., 2011*). Lichen planus represents an autoimmune lymphocytic response that may involve HSPs in its initiation and/or its persistence (*Sugerman et al., 2002*).

MATERIALS AND METHODS

Forty Lichen Planus patients were recruited for this from the Dermatological Department, Faculty of Medicine, Cairo University Hospitals. Twenty, age-matched, healthy subjects were included in the study as controls. They were classified into three groups:

Group I: Twenty healthy controls, 11 males and 9 females with similar demographic characteristics.

Group II: Twenty patients with the diagnosis of oral lichen planus, 14 males and 6 females.

Group III: Twenty patients with the diagnosis of cutaneous lichen planus, 19 males and 1 female.

Selection of Subjects and Diagnosis of Lichen Planus:

Diagnosis of lichen planus was confirmed based on the typical clinical and histopathological picture of lichen planus. The study included both male and female lichen planus patients regardless of their age. These patients had not received any treatments for at least one month before the study.

In addition, patients on phototherapy or receiving the drug for lichen planus within one month or patients suffering from cutaneous tumors or apparent autoimmune diseases were excluded.

Ethics Approval:

This study was approved by the Ethical Committee of Kasr Alainy Medical Hospital. Written informed consent was obtained from each participant.

Methods:

All subjects of the study were conducted to:

1. Full history was taken and a full clinical examination was done.
2. Tissue biopsies were obtained from patients and control groups for measuring gene expression of GRP78, ATF6 and Beclin-1 genes (by RT-PCR):

Quantitative real-time PCR gene expression of GRP78, ATF6 and Beclin-1 genes

- Total RNA was extracted from tissues biopsies homogenated using the RNeasy Purification Reagent (*Promega, Madison, WI, USA*) according to the manufacturer’s protocol. The extracted RNA was quantified

by spectrophotometry (*JENWAY, USA*) at 260 nm.

- The extracted total RNA (0.5–2 µg) was used for cDNA conversion using high capacity cDNA reverse transcription kit (*#K1621, Fermentas, USA*). The cDNA was generated from extracted total RNA with 1 µL (20 pmol) of antisense primer and 0.8 µL of superscript AMV reverse transcriptase for 60 min at 37°C.

- Real-time qPCR amplification and analysis were performed using SYBR® Green PCR Master Mix Reagents Kit (*Catalog Number 4309155*) and Applied Biosystem Instrument with software version 3.1 (*StepOne™, USA*). The PCR primers used were designed with Gene Runner Software (*Hastings Software Inc., Hastings, NY, USA*) from RNA sequences in GenBank (Table 1).

Table 1: The primer sequence of the studied genes (*GRP78, ATF6 and Beclin-1*).

Gene	Primer sequence	Gene bank accession No
<i>Beta actin (House keeping)</i>	Forward: 5'-ATCACCATCTTCCAGGAGCG -3' Reverse: 5'-CCTGCTTACCACCTTCTTG-3'	NM_0011101.3
<i>GRP78</i>	Forward: 5'-TGGGTCGACTCGAATTCCAAAG-3' Reverse: 5'-GTCAGGCGATTCTGGTCATTGG-3'	NM_005347.5
<i>ATF6</i>	Forward: 5'-GTCCCAGATATTAATCACGGA-3' Reverse: 5'-TTATTTAAGCCTCTGGTTCTCTGAC-3'	NM_007348.4
<i>Beclin-1</i>	Forward: 5'-ACCGTGTCACCATCCAGGAA-3' Reverse: 5'-GAAGCTGTTGGCACTTTCTGT-3'	NM_001313998.2

- All of the primer sets had a calculated annealing temperature of 60°C. Quantitative RT-PCR analysis was performed in duplicate in a 25-µL reaction volume consisting of 2× SYBR Green PCR Master Mix (*Applied Biosystems, USA*), 900 nM of each primer, and 2–3 µL of cDNA. The amplification conditions were 2 min at 50°C, 10 min at 95°C, and 40 cycles of denaturation at 95°C for 15 s and annealing/extension at 60°C for 10 min. Data from the real-time assays were calculated by Sequence Detection Software version 1.7 (*PE Biosystems, Foster City, CA, USA*). The relative expression level of GRP78, ATF6 and Beclin-1 was calculated by the comparative Ct method as stated by

the manufacturer recommendations (*Applied Biosystems, USA*).

Statistical Analysis:

Data were coded and entered using the statistical package SPSS version 22 Chi² test was used when comparing non-parametric data. Mann Whitney test was used to compare the duration of the disease. Numerical data were summarized using mean and standard deviation. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons post hoc test when comparing more than 2 groups. Correlations between quantitative variables were done using Pearson correlation coefficient, and

spearman correlation with course and duration (Chan, 2003).

RESULTS

This study reveals multiple results, the following results are the most prominent. The age of both cutaneous and oral lichen patients showed a statistically significant decrease compared to the normal control

subjects ($p=0.02$), while no significant difference between the cutaneous lichen patient and those having oral lichen (p -value = 1). The incidence of both cutaneous and oral lichen planus is more common in male patients. The duration of the disease is significantly higher in oral lichen than in cutaneous lichen (p value= 0.001) (Table 2).

Table (2): Demographic and clinical data among the studied groups.

Variable	Control Group (I) n=20	Cutaneous lichen Group (II) n=20	Oral lichen Group (III) n=20	P1 value	P2 value	P3 value
Age (years)	50 \pm 6.9	40.6 \pm 14.8	40.5 \pm 9.6	0.02	0.02	1
Sex Male Female	11(55%) 9(45%)	19(95%) 1(5%)	14(70%) 6(30%)	0.015		
Course Progressive n (%) Stable n (%)		11(55%) 9(45%)	15(75%) 5(25%)			0.1
Duration Minimum Maximum Median		1ms 48ms 6ms	2ms 96ms 24ms			0.001

Data were expressed as Mean \pm SD, p value <0.05 was significant. (P1) Denotes significant difference of cutaneous lichen group (II) versus control group (I). (P2) Denotes significant difference of oral lichen group (III) versus control group (I). (P3) Denotes significant difference of cutaneous lichen group (II) versus oral lichen group (III).

Table 3: Gene expression of the studied genes (GRP78, ATF6 and Beclin-1) by RT-PCR technique among studied groups.

	Control Group(I) n=20	Cutaneous lichen Group (II) n=20	Oral lichen Group (III) n=20	P1 value	P2 value	P3 value
GRP78	1.03 \pm 0.05	5.7 \pm 2.5	6.9 \pm 1.9	<0.001	<0.001	0.09
ATF6	1.09 \pm 0.01	5.9 \pm 2.07	6.2 \pm 2.2	<0.001	<0.001	0.93
Beclin-1	1 \pm 0.01	6.2 \pm 2.5	6.6 \pm 2.02	<0.001	<0.001	0.9

Data were expressed as Mean \pm SD, p value <0.05 was significant. (P1) Denotes significant difference of cutaneous lichen group (II) versus control group (I). (P2) Denotes significant difference of oral lichen group (III) versus control group (I). (P3) Denotes significant difference of cutaneous lichen group (II) versus oral lichen group (III).

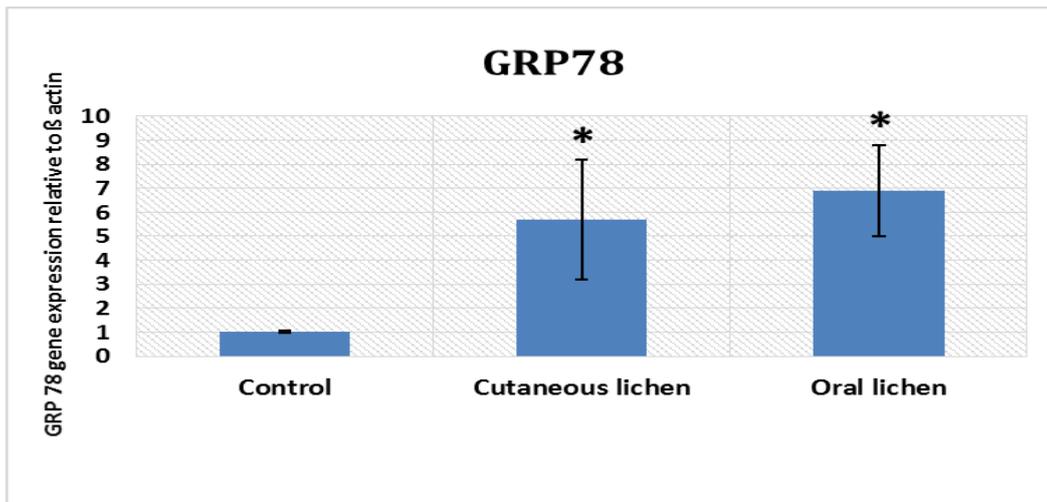


Fig. (1): GRP78 mean levels among different studied groups

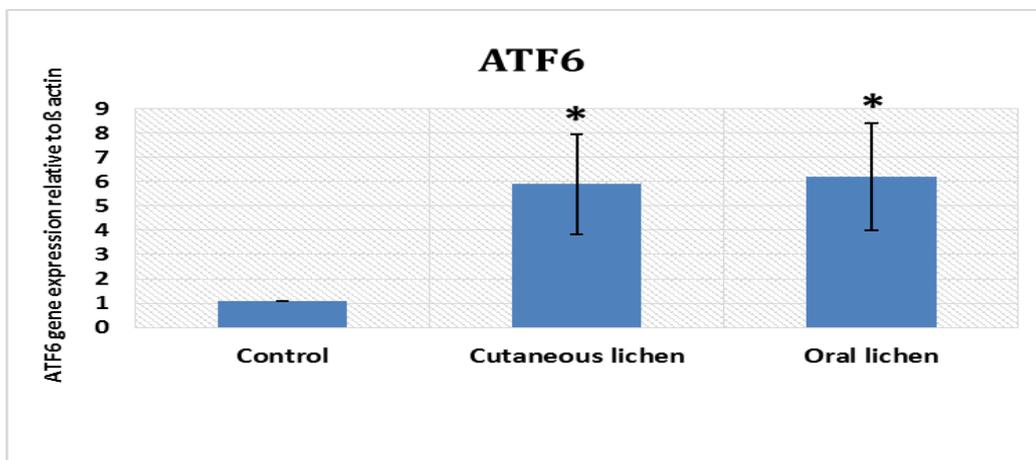


Fig. (2): ATF6 mean levels among different studied groups

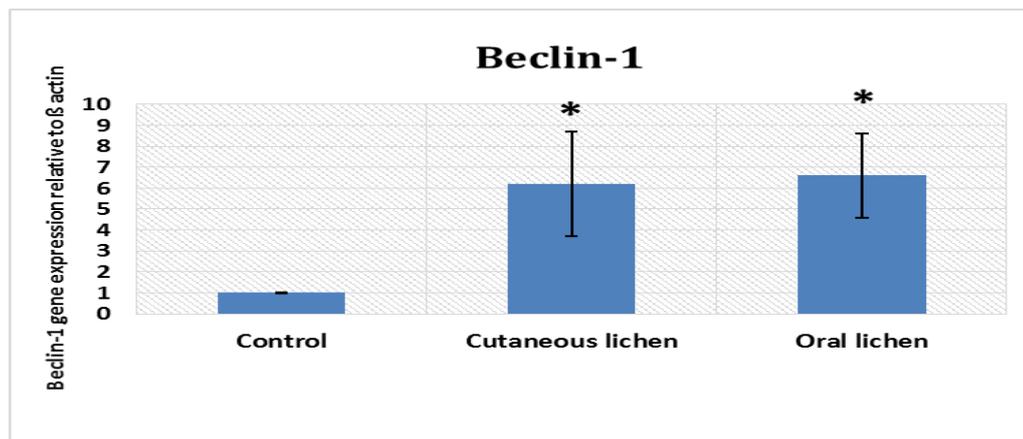


Fig. (3): Beclin-1 mean levels among different studied groups

The gene expression of studied genes (GRP78, ATF6 and Beclin-1) shows a significant increase in both cutaneous and oral lichen planus patients compared to the normal control (p-value < 0.001 for each studied gene). While patient group (oral & cutaneous) comparison shows no significant difference between different studied genes (GRP78, ATF6 and Beclin-1 p-value =0.09, p-value =0.93 and p-value =0.9 respectively) (Table 3 & Fig. 1-3).

Table 4: correlation analysis between different studied parameters in cutaneous lichen patients.

		GRP78	ATF6	Beclin1
GRP78	r	1	0.517**	0.689**
	P value		0.001	0.000
ATF6	r	0.517**	1	0.551**
	P value	0.001		0.000
Beclin1	r	0.689**	0.551**	1
	P value	0.000	0.000	

***. Correlation is significant at the 0.01 level (2-tailed).*

r = correlation coefficient, $r < 0.3$: no correlation, $r = 0.3 - < 0.5$: weak correlation, $r = 0.5$: fair correlation, $r = > 0.5 - 0.75$: good correlation, $r > 0.75$: very good correlation.

Table 5: correlation analysis between different studied parameters in oral lichen patients.

		GRP78	ATF6	Beclin1
GRP78	r	1	0.820**	0.766**
	P value		0.000	0.000
ATF6	r	0.820**	1	0.771**
	P value	0.000		0.000
Beclin1	r	0.766**	0.771**	1
	P value	0.000	0.000	

***. Correlation is significant at the 0.01 level (2-tailed).*

r = correlation coefficient, $r < 0.3$: no correlation, $r = 0.3 - < 0.5$: weak correlation, $r = 0.5$: fair correlation, $r = > 0.5 - 0.75$: good correlation, $r > 0.75$: very good correlation.

The correlation analysis between different studied parameters reveals a good correlation in cutaneous lichen patients (Table-4) and a very good correlation in oral lichen patients which means a correlation between ER stress and autophagy (Table-5).

DISCUSSION

Lichen planus (LP) is an immune-mediated, chronic inflammatory disease that can affect different parts of your body, including skin, mucous membranes and nails with characteristic two variants, cutaneous and oral lichen planus. Cutaneous LP could be self-limiting and pruritic, while the oral LP lesions are commonly chronic, non-remissive and could be a source of morbidity like malignant transformation (Parihar *et al.*, 2015 & Alrashdan *et al.*, 2016). Although the defined aetiology remains unknown; immune dysregulation has been reported to play a critical role, with the disease being the outcome of the influence of various extrinsic antigens or altered self-antigens (Conrotto *et*

al., 2018). The immunopathogenesis of lichen planus may include antigen presentation, T cells activation and migration, and the apoptosis dysregulation of keratinocytes (Zhou *et al.*, 2012). Briefly, activated T cells (CD4⁺ helper T cells & CD8⁺ cytotoxic T cells) may broker the keratinocytes apoptosis through multiple cytokine mediators (Zhang *et al.*, 2017).

Autophagy is a crucial mechanism for cellular homeostasis by degradation of dysfunctional or long-lived proteins and organelles (Wang *et al.*, 2015), Also autophagy provides a modulatory process for adaptive immunity by the development and homeostasis of the immune system and antigen presentation (Levine *et al.*, 2011). Moreover, autophagy interestingly mediates the normal development of B cell and T cell lymphocyte populations (Clarke *et al.*, 2015). Through its major inhibitory pathway Akt/mTOR, autophagy has been implicated in autoimmune diseases (Zhang *et al.*, 2017).

Endoplasmic reticulum stress “ER stress” refers to a number of biological, psychological, or pathological stimuli that can perturb protein folding in the ER, leading to the accumulation of unfolded or misfolded proteins in the ER lumen (Prans *et al.*, 2017) and recently, ER stress and the UPR have been linked to a variety of pathologies including autoimmune and neurodegenerative diseases (Cao *et al.*, 2016). Activating transcription factor 6 (ATF6) is one of three major transducers for sensing ER stress that has been identified on the membrane of the ER. The others are RNA-dependent protein kinase-like ER kinase (PERK) and inositol-requiring ER-to-nucleus signal kinase 1 (IRE1) (Salminen *et al.*, 2020).

Glucose-regulated protein 78 (GRP78), also referred to as BiP/HSPA5, is a member of the 70 kDa heat shock protein (HSP70) family and is evolutionarily conserved from yeast to humans (Tsai and Lee, 2018). GRP78 is associated with IRE-1, ATF-6 and PERK and is responsible for ensuring that newly synthesized polypeptides entering the ER are properly folded into functional proteins. Accumulation of misfolded/unfolded proteins within the ER, GRP78 dissociates from IRE1, ATF6, and/or PERK activating the UPR (Ibrahim *et al.*, 2019). Moreover, increasing evidence has suggested that GRP78 participates in antibody generation, T cell proliferation, and proinflammatory cytokine production (Park *et al.*, 2014).

In our study, cutaneous and oral lichen planus patients show a significant increase in GRP78 gene expression in comparison to the control group but no significant difference in comparison to each other. These results match a study done on GRP78 expression in OLP which revealed an increased expression of GRP78 in the basal and suprabasal cells of the epithelium of OLP suggesting implication for GRP78 in OLP pathogenesis (Tyagi *et al.*, 2012). Moreover, Park *et al.*, detected that extracellular GRP78 level was significantly high in rheumatoid arthritis (RA) joints,

which contributed to the development of auto-reactive T cells and increased the production of IL-17 and TNF- α in RA synovial mononuclear cells (Park *et al.*, 2014). On the other hand, a previous study found that GRP78 has anti-inflammatory properties partially dependent on the downregulation of HLA-DR (Human Leukocyte Antigen – DR isotype) and co-stimulatory molecules and the predominant production of IL-10 (Yoshida *et al.*, 2011).

Upon ER stress, the inactive form of ATF6 is transported from ER membrane to the Golgi apparatus where it is activated by a two-step cleavage protease. The free active ATF6 migrates to the nucleus to activate transcription (Garg *et al.*, 2012). ATF6 controls the expression of the ER chaperone GRP78. Furthermore, ATF6 works in concert with PERK in transactivating the CHOP (CCAATenhancer-binding protein homologous protein) gene and thus contributes to the induction of those autophagy genes whose expression depends on CHOP. Therefore, activation of ATF6 during ER stress is of importance for autophagy induction, vesicle nucleation, and elongation of the phagophore (Yeganeh *et al.*, 2015).

This gets through and enforces our results which reveal a significant increase of ATF6 gene expression in diseased groups (oral and cutaneous) compared to normal control, however, there is no significant difference in ATF6 gene expression between cutaneous and oral lichen planus patients.

Beclin 1 regulates macroautophagy (autophagy) in eukaryotic cells through the localization of autophagic proteins to a pre-autophagosomal structure (PAS) (Kang *et al.*, 2011). That extremely showed in this study, regarding the level of Beclin-1 gene expression it showed a significant increase in diseased groups (oral and cutaneous) compared to normal control, but there is no significant difference in Beclin-1 gene expression between cutaneous and oral lichen planus patients.

There is a lack of information regarding the level of Beclin-1 gene

expression in LP. Yet our findings go with a study performed by Wu *et al.*, 2017 which detected that the mean levels of Becline-1, LC3 and p62 mRNA were significantly higher in SLE patients than the controls. Also, Wu *et al.*, 2017 suggested that autophagosomes formation was activated and their degradation was blocked in SLE.

Collectively from the previous findings, we can conclude that there is a correlation between ER stress and autophagy with the occurrence of lichen planus. These findings put ER stress and autophagy in either a compensatory mechanism or induction mechanism for lichen planus and so a target point to control or treat lichen planus.

Conclusion:

The results of the study suggested that the level of autophagy and endoplasmic stress is increased with lichen planus either oral or cutaneous. This increase may represent an inductor or compensatory (protective) mechanism to lichen planus. ER Bip chaperone (GRP78) may represent a clue constructive point in lichen planus disease development.

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ARABIC SUMMARY

مستوى الإلتهام الذاتي في مرض الحزاز المسطح وكذا دور إجهاد الشبكة الإندوبلازمية

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يعد الحزاز المسطح مرض التهابي مزمن شائع بوساطة الخلايا التائية يصيب الجلد و/ أو الأغشية المخاطية. ويشترك الإلتهام الذاتي، الناجم أيضا عن الخلايا التائية، كسبب مناعى لحدوث النوع الفموي من الحزاز المسطح. بكلن-1 (Beclin-1) هو أحد دلالات الإلتهام الذاتي والذي يقوم بدور حاسم في عملية الإلتهام الذاتي. يزيد تخليق بروتينات الصدمة الحرارية (HSP) استجابة للعديد من الضغوطات كونها المرافقين الجزيئيين (تشبيرون). تمتلك HSP دور مهم في عملية إجهاد الشبكة الإندوبلازمية (إجهاد ER). كما يفترض أن HSP تشارك في بدء وربما استمرار الحزاز المسطح من خلال استجابة الخلايا للمفاوية المناعية الذاتية. تعتبر البروتين المنظم للجوكوز 78 (GRP78) هو أحد أنواع HSP والذي قد يلعب دورا كبيرا في حدوث الحزاز المسطح. بالإضافة أيضا، يعد عامل النسخ المنشط-6 (ATF6) هو أحد مستشعرات مسار إجهاد ER الذي قد يمثل رابطا بين إجهاد ER والإلتهام الذاتي. أجريت الدراسة على 40 مريضا بالحزاز المسطح و20 شخصا معافا من الحزاز المسطح. وقد تم فحص التعبيرات الجينية لكل من ATF6, GRP78 و Beclin-1 بواسطة تفاعل البوليميراز المتسلسل في الوقت الفعلي (Real-time PCR). وقد أظهرت الدراسة زيادة كبيرة في التعبير الجيني لكل من ATF6, GRP78 و Beclin-1 في مرضى الحزاز المسطح الفموي والجلدي مقارنة بمجموعة الأشخاص الأصحاء. الإستنتاج: تشير الدراسة الى زيادة في دلالات الإلتهام الذاتي والإجهاد الشبكي الإندوبلازمية والذي بدوره ربما يكون جزء من آلية حدوث وربما الوقاية من مرض الحزاز المسطح.