

Assessment of the Effect of Metabolic Syndrome on the Autophagy Marker LC3 in Psoriasis Vulgaris Patients: A Cross-Sectional Study

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Purpose: Psoriasis vulgaris, one of the most prevalent chronic inflammatory skin diseases, is associated with metabolic syndrome (MetS). Autophagy, an intracellular degradation system is essential for cell survival and differentiation, and its dysfunction may contribute to metabolic diseases. A cross-sectional study was conducted on 38 psoriasis vulgaris patients and 16 healthy control subjects to 1) Assess immunohistochemical (IHC) expression of microtubule-associated protein light chain 3 (LC3); 2) Evaluate the relationship between Psoriasis Area Severity Index (PASI) score, and LC3 expression.

Patients and Methods: PASI score was evaluated for all psoriasis patients. Lipid profile, blood sugar, and CRP were done for all patients and controls. A punch biopsy was taken from lesional and perilesional skin of psoriasis patients and normal skin of the controls. Tissue sections were prepared. IHC LC3 staining was done and evaluated.

Results: LC3 was nearly absent, in the epidermis of the lesional skin of psoriasis while it was strong among control ($p=0.001$). LC3 expression in the lesional skin of psoriasis vulgaris was lower than its expression in perilesional ($p=0.001$). However, LC3 expression was not significantly changed with PASI or the presence/absence of MetS.

Conclusion: A potential link between psoriasis vulgaris and autophagy as assessed by LC3 could be present. LC3 was down-regulated in psoriasis lesions than in normal skin. However, its expression did not change with PASI or MetS. An autophagy enhancer might be used as a possible therapeutic target in psoriasis vulgaris patients.

Keywords: psoriasis vulgaris, Psoriasis Area Severity Index score, PASI score, metabolic syndrome, autophagy, microtubule-associated protein light chain 3, LC3

Introduction

Psoriasis vulgaris is a common chronic recurrent inflammatory skin disease with a strong genetic predisposition,¹ affecting 2% of the general population. It has a multifactorial etiology including genetic, epigenetic, and environmental factors, leading to keratinocyte proliferation and immune cell infiltration, mostly T cell.² An association between psoriasis and metabolic diseases such as obesity, diabetes, and cardiovascular diseases (CVDs) has been recognized.³ The prevalence of MetS increases in psoriasis patients,⁴ and the severity (PASI score) and duration of psoriasis are positively correlated with the prevalence of MetS and its components.³

Autophagy is an intracellular process by which a part of the cytoplasm is degraded through the lysosomes. It is important for cell survival and differentiation. Autophagy dysfunction may be an important contributor to metabolic diseases such

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as diabetes, obesity, and MetS.⁵ Defects in autophagy may lead to inflammation and keratinocyte proliferation, which are the two main pathological features of psoriasis.⁶ However, no previous study investigates tissue autophagy in psoriasis patients with MetS.

One of the most specific markers of autophagy monitoring is LC3.⁷ In normal skin, LC3 is expressed in all epidermal layers with the strongest expression in the granular cell layer.⁸ In keratinocyte, immunofluorescence analysis showed perinuclear localization of LC3.⁹ LC3 expression is reduced or absent in the epidermis of psoriasis patients.⁸ Moreover, the ATG16L1 (2q37) gene which is responsible for the formation of the ATG16L1 protein that is a key protein in the autophagy pathway, and polymorphisms in this gene have been associated with the development of psoriasis.¹⁰

Therefore, this study aimed to assess immunohistochemistry (IHC) expression of LC3 in the skin of psoriasis vulgaris patients compared with that in the controls; and to evaluate the relationship between autophagy as assessed by LC3 expression, MetS and psoriasis vulgaris severity evaluated by PASI score.

Materials and Methods

The study included 38 patients of psoriasis vulgaris and 16 healthy individuals (control) who were attending the Dermatology Outpatient Clinic of Sohag University Hospitals, Sohag, Egypt; from November 2017 to April 2019. Sample size was determined from the previous studies in the literature that reported the prevalence of MetS varies between 24% and 60% in psoriasis vulgaris patients. The study was approved by the Research and Ethical Committee of Sohag Faculty of Medicine. A written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki. The diagnosis of psoriasis was established according to the clinical findings and confirmed by routine H&E stained biopsy sections.

Inclusion Criteria

Only patients with typical clinical findings of psoriasis vulgaris (diagnosis of psoriasis duration \geq 6 months) and aged 18 years or more were included in the study.

Exclusion Criteria

Patients with other clinical varieties of psoriasis, patients receiving topical/systemic treatment for 1 month before enrollment, pregnant or lactating women, and patients with advanced hepatic or renal failure were excluded.

All participants were subjected to:

1. Initial evaluation:

The general examination included weight, height, body mass index (BMI), blood pressure, and waist circumference (WC) which was measured immediately below the lowest ribs.¹¹

2. Dermatological evaluation:

The Psoriasis Area Severity Index (PASI) was used for patients' evaluation.¹² It is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement. The net result of PASI ranges from 0 to 72. The severity of plaque psoriasis was graded as mild (PASI \leq 10) and moderate to severe ($>$ 10).¹³

3. Laboratory investigations:

3-1. Fasting blood glucose level.

3-2. Lipid profile assessment: Blood samples were taken after overnight fasting (12–14 hrs) to assess triglyceride (TGs), total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

3-3. C-reactive protein (CRP) and serum uric acid: as markers of chronic inflammation.

4. Metabolic syndrome diagnosis:

Diagnosis of MetS was done using the Joint Interim Statement (JIS),¹⁴ with Egyptian cutoffs¹⁵ as any three of the following: elevated WC $>$ 100.5 cm in men and $>$ 96.25 cm in women; TGs 150 mg/dl or greater; HDL – cholesterol $<$ 40 mg/dl in men and $<$ 50 mg/dl in women; blood pressure \geq 130/85 mmHg; and fasting glucose \geq 100 mg/dl.

5. Skin biopsy:

Four mm punch biopsy was obtained from lesional and non-lesional skin of psoriasis patients, and normal skin of control individuals. Biopsies were fixed in 10% neutral formalin and paraffin-embedded serial sections were prepared.

5-1. Hematoxylin and Eosin (H&E) staining:

- Sections of 4µm thick from formalin-fixed paraffin-embedded tissue blocks were used for H&E staining.

5-2. LC3 IHC staining:

- Sections of 4µm thick were cut and mounted on saline-coated glass slides and the slides were incubated overnight at room temperature for accurate adhesion of the tissues to the slides. The slides were de-paraffinized in xylene for 20 mins, rehydrated in down-regulated alcohol, then rinsed in distilled water. Endogenous peroxidase activity was blocked by incubation of tissue sections in 0.6% hydrogen peroxide for 10 mins.
- The tissue sections were washed twice in diluted phosphate-buffered saline (PBS), then antigens were retrieved by boiling the sections twice in citrate buffer, pH 6.0 using a microwave at mid-high power for 10 mins each, followed by cooling down to room temperature for 30 mins. After washing twice in PBS, tissue sections were treated with superblock. Tissue sections were rinsed twice with PBS and incubated with rabbit anti LC3B monoclonal antibody (D11, XP® #3868T, Cell Signaling Technology) at a concentration of 1:3200 for overnight at room temperature.
- Excess reagent was thrown off and tissue sections were rinsed twice in PBS, incubated with streptavidin for 10 mins at room temperature, washed twice in PBS, and exposed to a freshly prepared 3,3'-diaminobenzidine tetrahydrochloride solution (DAB) for 5–10 mins to yield an insoluble brown deposit (Chromogen detection system was purchased from Dako). Finally, the sections were counterstained with hematoxylin.
- Sections from astrocytoma were used as a positive control.
- LC3-IHC expression was analyzed independently of the clinico-pathological data. The analysis was done with two blind pathologists.

5-3. Analysis of LC3:

- The immune-reactive score (IRS) was determined by multiplying an estimate of staining quantity which is the percentage of the immune-reactive cells with an estimate of the staining intensity.¹⁶ Staining quantity is scored as follows: no staining = 0; positive staining in ≤25% of cells counted = 1; positive in >25% and ≤50% = 2; positive in >50% and ≤75% = 3; positive in >75% = 4. Staining

intensity is scored on a scale of 0–3 where: no staining = 0; weak = 1; moderate = 2; strong = 3. An IRS of 0 was considered negative; 1–4 was considered weak; 6–8 was moderate, and 9–12 was considered strong.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software (version 22). Quantitative variables were presented as mean± standard deviation (SD) when results were normally distributed and as median (interquartile range 25th-75th) when results were not normally distributed. Categorical variables were expressed as percentages. For continuous variables, a comparison between two normally distributed variables independent samples' *t*-test was used, while the Mann–Whitney *U*-test was used to compare between two not normally distributed variables. Kruskal–Wallis test was used for comparison between more than 2 groups. For categorical variables, the Chi-square test was used. P-value ≤0.05 was considered significant.

Results

The current study was conducted on 54 participants (38 patients with psoriasis vulgaris and 16 healthy controls). Patients were mainly males; 27/38 (71.1%) with a mean age ± SD was 48.45±14.94 years. According to the PASI score, 19/38 (50%) of patients had mild psoriasis (≤10). The mean duration of psoriasis was 7.2±5.2 years. In comparison between patients and control as regard components of MetS, there was a statistically significant difference in systolic blood pressure (*p* <0.001), diastolic blood pressure (*p*=0.036) being higher in patients, and HDL (*p*<0.001) being lower in patients as compared to control. Other demographic data are shown in [Table 1](#).

MetS diagnosis was significantly higher in patients 16/38 (42.1%) as compared to control 4/16 (25%) (*p*=0.003). Patients had significantly higher WC (*p*=0.002), lower HDL (*p*=0.0004), and increased TGs (*p*=0.04) compared to control. Other data are shown in [Table 2](#).

H&E stained tissue sections from perilesional and lesional psoriatic skin from the patients and normal skin from the control group were examined and LC3 expression was assessed using IHC staining as shown in [Figure 1](#). A significantly higher expression LC3 expression was found in the skin of the control group (IRS was 12.0 and the range was 6.0–12.0) than in perilesional, (IRS was 1.5

Table 1 Demographic Data of Psoriasis Vulgaris Patients and Control

	Psoriasis Patients (n=38)	Control (n=16)	P value
	Mean± SD Median (25 th -75 th) n (%)	Mean± SD Median (25 th -75 th) n (%)	
History:			
Age	48.45±14.94	45.38±14.04	0.486
Sex:			
• Male	27 (71.1%)	8 (50.0%)	0.122
• Female	11 (28.9%)	8 (50.0%)	
Residence:			
• Rural	29 (76.3%)	13 (81.3%)	0.756
• Sub-urban	4 (10.5%)	2 (12.5%)	
• Urban	5 (13.2%)	1 (6.3%)	
Occupation:			
• Not working	15 (39.5%)	8 (50.0%)	0.433
• Employee	6 (15.8%)	2 (12.5%)	
• Farmer	3 (7.9%)	3 (18.8%)	
• Worker	14 (36.8%)	3 (18.8%)	
Marital status:			
• Single	1 (2.6%)	0 (0%)	0.512
• Married	35 (92.1%)	16 (100.0%)	
• Widow	2 (5.3%)	0 (0%)	
Special habits:			
• No	21 (55.3%)	11 (68.8%)	0.797
• Cigarette	8 (21.1%)	2 (12.5%)	
• Shisha	5 (13.2%)	2 (12.5%)	
• Mixed (Cigarette + shisha)	4 (10.5%)	1 (6.3%)	
Smoking Brinkman index	515±336	460±120	0.882
Examination:			
Weight (kg)	76.08±15.58	73.63±9.76	0.563
Height (cm)	166.95±8.01	165.19±8.44	0.471
BMI	27.21±4.73	26.76±4.28	0.742
WC (cm)	100.97±15.62	92.69±10.27	0.057
Systolic blood pressure	125.53 (105.89–130)	110.63 (99.98–115)	<0.001*
Diastolic blood pressure	79.08 (72.29–85)	73.13 (70.04–79)	0.036*
Laboratory investigations:			

(Continued)

Table 1 (Continued).

	Psoriasis Patients (n=38)	Control (n=16)	P value
	Mean± SD Median (25 th -75 th) n (%)	Mean± SD Median (25 th -75 th) n (%)	
HDL	33.81±10.16	44.44±8.04	<0.001*
TGs	167.29 (141.26–182.5)	142.63 (66.74–157.5)	0.615
FBG	91.97 (30.63–95)	111.38 (75.15–105.5)	0.649
Serum UA	1.58 (0.5–2)	1.75 (0.45–2)	0.076
CRP	3.5 (3–6)	4 (4–6)	0.984

Note: *Statistically significant difference p<0.05.

Abbreviations: BMI, body mass index; WC, waist circumference; HDL, high-density lipoprotein; TGs, triglycerides; FBG, fasting blood glucose; UA, uric acid; CRP, C reactive protein.

and the range was 1.0–2.0) and lesional (IRS was 0.0 and the range was 0.0–1.0) skin of patients as shown in [Figure 2](#).

LC3 expression was significantly increased in the skin of the control group without MetS than in the skin of the control with MetS (IRS was 12 and 9 and the range was 6.75–12 and 3.75–12, respectively; p=0.003). However, there was no significant variation in lesional expression of LC3 between patients with MetS and patients without MetS (IRS was 0 and the range was 0.0–2.0 for each of them) as shown in [Figure 3](#).

Besides, no significant statistical difference in LC3 expression comparing in lesional skin of mild psoriasis

Table 2 Frequencies and Percentage of Different Criteria of MetS Among Patients and Control

	Psoriasis Patients (n=38)	Control (n=16)	P value
WC >100.5 (male) or >96.25 (female)	20 (52.63%)	4 (25%)	0.002*
Systolic blood pressure ≥ 130	13 (34.21%)	5 (31.25%)	0.09
Diastolic blood pressure ≥ 85	11 (28.94%)	4 (25%)	0.121
HDL <40 (male) or<50 (female)	31 (81.57%)	8 (50%)	0.0004*
TGs ≥ 150	17 (44.73%)	6 (37.5%)	0.04*
FBG ≥ 100	8 (21.05%)	4 (25%)	0.386
Diagnosis of MetS	16 (42.1%)	4 (25%)	0.003*

Note: *Statistically significant difference p<0.05.

Abbreviations: WC, waist circumference; HDL, high-density lipoprotein; TGs, triglycerides; FBG, fasting blood glucose; MetS, metabolic syndrome.

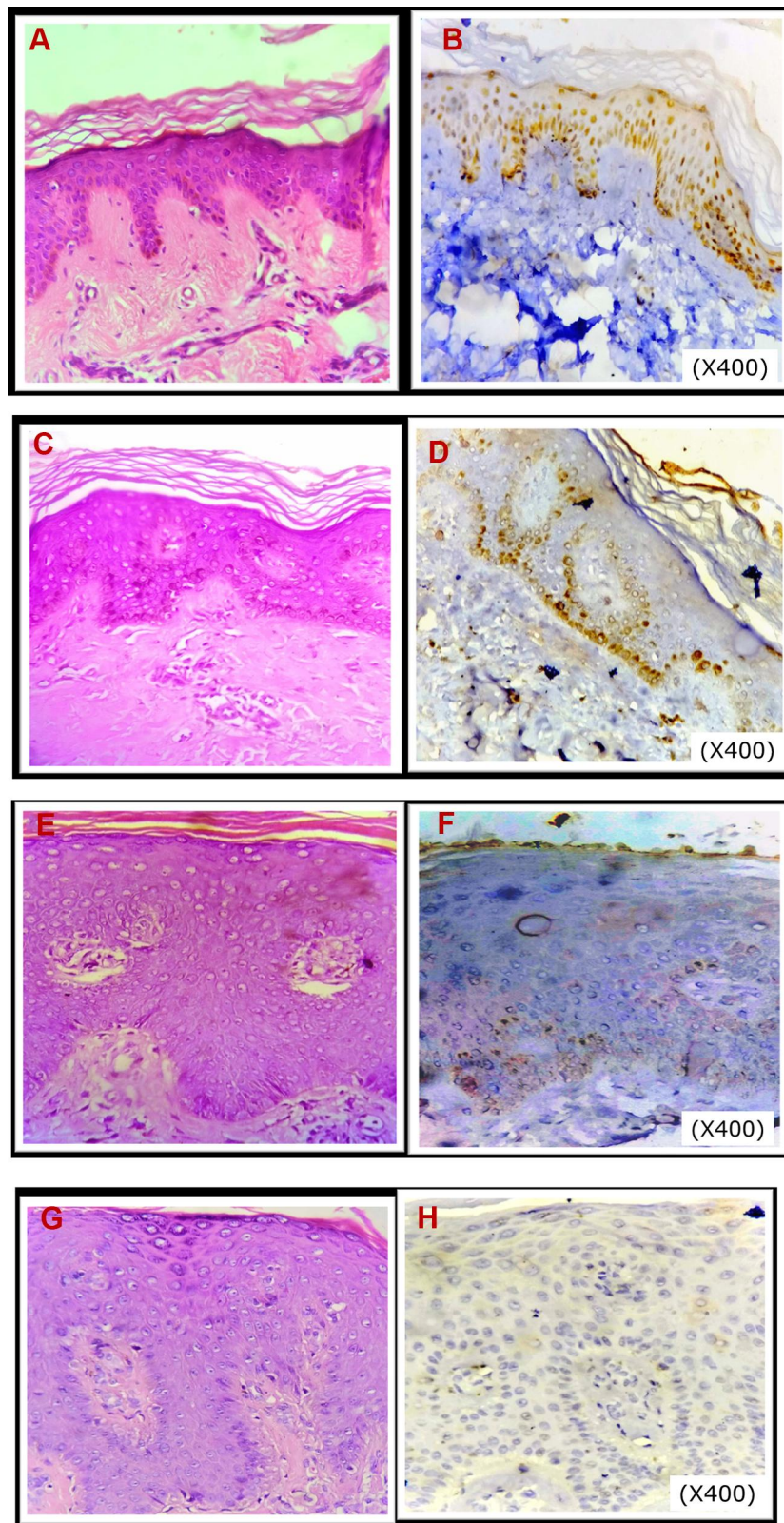


Figure 1 (A) Normal skin of control (H&E); (B) Normal skin of control showing strong expression of LC3; (C) Normally-looking perilesional skin (H&E); (D) Moderate expression of LC3 in perilesional skin; (E) Psoriatic lesional skin (H&E); (F) Psoriatic lesional skin with weak expression of LC3; (G) Psoriatic lesional skin (H&E); (H) Negative expression of LC3 in psoriatic lesional skin (x400).

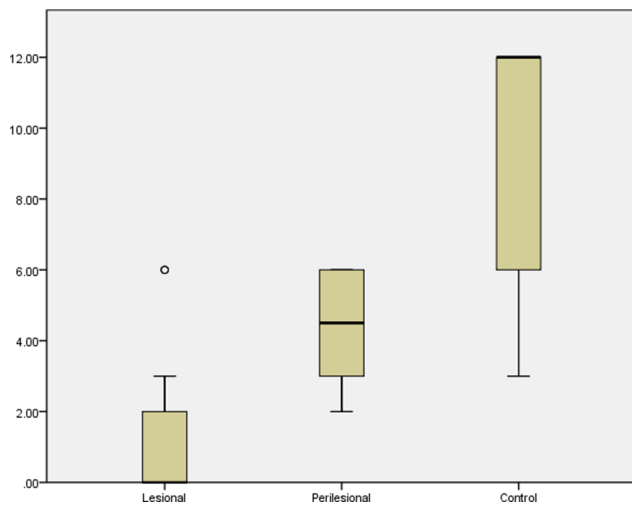


Figure 2 Expression of staining quality of LC3 by IHC in patients and control.

and that of moderate to severe psoriasis patients (IRS was 0 and the range was 0.0–2.0 for each of them) as shown in Figure 4.

Discussion

Psoriasis is considered not only a skin disease but also it is associated with several comorbidities such as MetS components. This association could be due to shared genetic factors and chronic inflammatory pathways between psoriasis and MetS.¹⁷ Autophagy study has been growing in skin diseases including psoriasis.¹⁸ In the same context, autophagy has a growing contribution to MetS pathogenesis.¹⁹

In the current study, LC3 expression was nearly absent, in the epidermis of lesional skin of psoriasis vulgaris patients while it was strong among the control group.

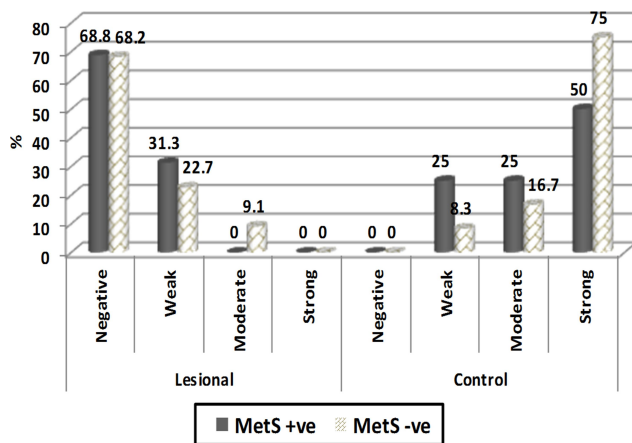


Figure 3 Expression of staining intensity of LC3 by IHC in lesional psoriasis with and without MetS and control with and without MetS.

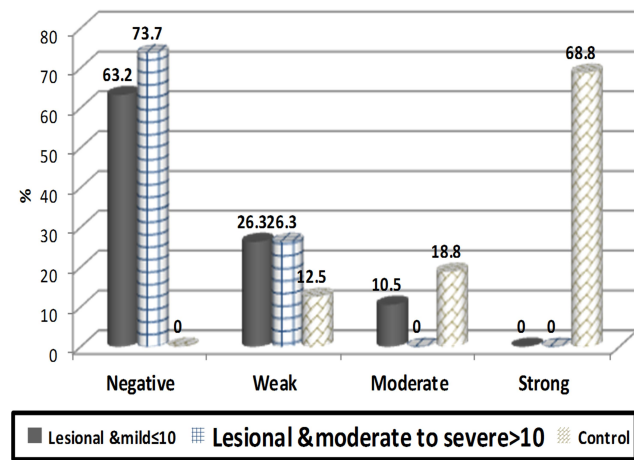


Figure 4 Expression of staining intensity of LC3 by IHC in lesional mild psoriasis patients (PASI≤10), lesional psoriasis moderate to severe patients (PASI>10) and the control group.

These results matched with a study that investigated the expression pattern of several autophagy markers (LC3, ULK1, BECN1, and ATG5-ATG12) in the skin of six psoriasis patients compared with the skin of five healthy volunteers. In lesional skin, LC3 expression was absent while ULK1 expression was increased in the whole epidermis except the parakeratotic layer, and BECN1 and ATG5-ATG12 expressions were increased in the suprabasal layer of the epidermis.⁹ Also, another study reported decreased LC3I and LC3II expression in lesional psoriatic skin compared to control, and this was accompanied by an increased expression of p62.²⁰ This p62 is usually degraded by the process of autophagy.²¹ This increased of p62 in psoriatic skin in comparison to control indicates a negative correlation between keratinocyte autophagy and p62 expression²² as p62 accumulation is considered an indicator for autophagy inhibition.²³

In contrast, a recent study showed increased expression of LC3 (LC3A/B, LC3A, LC3B) in psoriatic skin compared to control in a study included an equal number of patients and control (12 for each). This LC3 increased expression was associated with increase expression of BECN1 and ATG5, suggesting that autophagy is activated in psoriatic keratinocytes.²⁴ The difference in our findings from the aforementioned could be attributed to different antibodies used. LC3B was used in the current study, while LC3A/B, LC3A, LC3B were used in the other study. Also, the small sample size of the other study should be considered.

In the current study, the perilesional skin of psoriasis patients showed a significant reduction in LC3 expression

compared with healthy skin; however, it was still higher than its expression in the lesional skin of psoriasis patients. This is consistent with previous findings.⁹ This could reflect the early changes that occur in the normal-appearing skin around the psoriatic plaques. LC3 reduction could be due to the early inflammatory changes that occur in the perilesional skin.²⁵

Autophagy is a self-eating machinery system that is responsible for the degradation of old and damaged intracellular materials.²⁶ It plays a critical role in normal keratinocyte differentiation and melanocyte survival.¹⁸ The relationship between autophagy and inflammation is quite complex. The autophagy has a stimulant impact on the development and survival of inflammatory cells,²⁷ however, autophagy could be injurious to the tissues if inflammation is not properly controlled.²⁸

Autophagy could have a contributing role in psoriasis pathogenesis. Many pathogens have been linked to psoriasis including bacteria and viruses.²⁹ In the same context, autophagy has an important role in eliminating these pathogens. So autophagy dysfunction could potentiate the action of these pathogens as a triggering factor for psoriasis development.³⁰ A polymorphism in the Atg16L1 gene has been linked to psoriasis development which is essential for the autophagy pathway.¹⁰ This Atg16L1 gene product has a vital role in dealing with bacterial pathogens and antigen presentation, which could be responsible for psoriasis triggering.⁶ Therefore, autophagy dysfunction not only triggering psoriasis but also its inhibition could be responsible for aggravating the inflammatory process involved in psoriasis pathogenesis.²⁰

In the current study, LC3 expression was significantly increased in the skin of control without MetS than the skin of control with MetS, suggesting that the presence of MetS could suppress autophagy in normal skin. However, there was no significant variation in LC3 expression in the lesional skin of psoriasis patients with/without MetS. No previous reports explore the relationship between MetS and autophagy in psoriasis vulgaris patients. Abnormal autophagy regulation in the skin could predispose to MetS development and vice versa.³¹ MetS could have different actions on different tissues as regards autophagy including autophagy reduction in liver tissue and activation in adipose tissue in patients with MetS.¹⁹ Autophagy dysfunction could contribute to the development of metabolic disorders and restoration of its function could have therapeutic benefits.⁵

In the current study, LC3 expression did not change with the severity of psoriasis as assessed by PASI score. There was no significant difference in LC3 expression compared to mild and moderate to severe patients. There are no previous reports about the relation between LC3 expression and the severity of psoriasis. This could be partially due to the non-significant difference in CRP comparing psoriasis patients and control although being higher in psoriasis patients. This could reflect the relatively low inflammatory mediators in the patients of the current study. Skin inflammation in psoriasis patients is usually accompanied by systemic inflammation and progressively increased with increasing psoriasis severity.³² CRP might be considered a good indicator of psoriasis severity and showed a significant decrease with treatment.³³

There are several limitations of our study; the study sample had a relatively small size. Autophagy activity assessment was done with the use of only one marker (LC3). Therefore, future studies with larger sample size may be needed. It will be better to use more tools in autophagy assessment like transmission electron microscopy for the auto-phagosome demonstration which is the gold standard for autophagy monitoring. We could also use other autophagy markers with IHC like Beclin 1, p62/SQSTM1. It will be also of value to correlate the autophagy assessment and degree of T cell infiltration and the level of oxidative stress in psoriasis patients. A better understanding of these relationships may lead to the development of novel targets for therapeutic purposes.

Conclusions

There could be a potential link between psoriasis vulgaris and autophagy marker LC3 with lower skin expression in patients than in control. However, its expression did not change with severity or MetS. Autophagy enhancer might be used as a possible therapeutic target.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The clinical trial was approved by the ethical and scientific research committee of Sohag University, Sohag, Egypt.

Consent to Participate

A written informed consent was obtained from all participants for the clinical study participation.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest for this work.

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