

Toll-Like Receptor Expression in Patients with Chronic Eczema

Andrii A. Dashchuk, Maryna M. Mishyna, Andrii M. Dashchuk, Yevheniia I. Dobrzanska

Kharkiv National Medical University, Kharkiv, Ukraine

Dermatol Rev/Przegl Dermatol 2026, 113, 13–17
DOI: <https://doi.org/10.5114/dr.2026.162088>

CORRESPONDING AUTHOR:

Andrii A. Dashchuk
Kharkiv National
Medical University
Kharkiv, Ukraine
E-mail:
aadashchuk.po24@knmu.edu.ua

ABSTRACT

Introduction: Chronic eczema is a major challenge in dermatology due to its high prevalence, severe course, frequent relapses, significant burden affecting patients of different ages and both sexes. Effective treatment requires understanding environmental factors, especially microbial influences, which affect the patient's condition. These triggers are detected and mediated by transmembrane Toll-like receptors located in barrier tissues.

Objective: To investigate changes in Toll-like receptor 2 and Toll-like receptor 4 expression during recurrence of chronic eczema before and after treatment.

Material and methods: The study included 80 patients with chronic eczema (54 women, 26 men; aged 24–81 years) without severe somatic or infectious diseases and a control group of 20 individuals. Peripheral blood Toll-like receptor 2 and Toll-like receptor 4 expression was measured by flow cytometry using monoclonal antibodies conjugated with phycoerythrin.

Results: The study demonstrated increased colonization of eczema lesions with *Enterococcus faecalis* and *Streptococcus pyogenes*. Toll-like receptor 2 expression was elevated across all age groups and reached the highest values in men aged 61–81 years (118.00 ± 9.54 conventional units), particularly in patients with prolonged disease duration (15–20 years) and very severe eczema. Lower Toll-like receptor 2 expression was observed in patients with shorter disease duration. Toll-like receptor 4 expression was elevated in both men and women aged 41–60 years. Following treatment, Toll-like receptor 2 expression decreased to values comparable to controls, whereas Toll-like receptor 4 expression declined but remained at the upper limit of the reference range in men aged 41–60 years.

Conclusions: Toll-like receptor 2 and Toll-like receptor 4 expression was associated with eczema severity, disease duration, and patient age. Toll-like receptor 2 may represent a marker of disease activity and treatment response, whereas persistent Toll-like receptor 4 expression after therapy may reflect ongoing immune activation or skin barrier repair processes.

Key words: chronic eczema, Toll-like receptors, TLR2, TLR4.

INTRODUCTION

Despite substantial advances in the diagnosis and treatment of skin diseases, the incidence of allergic dermatoses remains high and continues to increase

worldwide. Chronic eczema represents one of the most common inflammatory dermatoses and accounts for up to 40% of all dermatoses [1]. Owing to its chronic relapsing course, tendency toward dissemination, re-

sistance to conventional therapy, and considerable impact on quality of life, chronic eczema remains a major challenge in contemporary dermatology [2].

The pathogenesis of chronic eczema is complex and involves interactions between epidermal barrier dysfunction, immune dysregulation, environmental factors, and microbial colonization [3]. Impaired skin barrier function facilitates the penetration of allergens, irritants, and pathogens into the skin, resulting in activation of innate and adaptive immune responses [4]. Among the key mediators involved in these processes are Toll-like receptors (TLRs), a family of transmembrane pattern-recognition receptors expressed on keratinocytes and immune cells within barrier tissues, including the skin and mucous membranes [5].

TLRs recognize pathogen-associated molecular patterns derived from microorganisms and participate in the initiation and regulation of inflammatory responses [6]. Increasing evidence indicates that TLRs are involved in the pathomechanisms of both infectious and non-infectious inflammatory diseases [7, 8]. However, their role in chronic eczema, particularly in relation to microbial dysbiosis and skin barrier impairment, remains insufficiently understood [9].

Previous studies demonstrated that disturbances in skin microbiocenosis in chronic eczema are associated with enhanced pathogenicity resulting from interactions between bacteria and microscopic fungi. Moreover, fungal colonization may contribute to sensitization, suppression of cellular immune responses, and progression of inflammatory skin disease [10].

To date, the role of TLR expression in the development and clinical course of chronic eczema under the influence of microbial factors has not been fully elucidated. Furthermore, data regarding changes in TLR expression before and after treatment in patients with chronic eczema remain limited.

OBJECTIVE

To investigate changes in TLR2 and TLR4 expression during recurrence of chronic eczema before and after treatment.

MATERIAL AND METHODS

The main group consisted of 80 patients with chronic eczema: 54 women and 26 men, aged 24–81 years. Patients in the main group were divided according to age: group 1 – 24–40 years ($n = 16$), group 2 – 41–60 years ($n = 38$), and group 3 – 61–81 years ($n = 26$). According to disease duration, the patients were divided into 6 subgroups: < 1 year ($n = 6$), 1–3 years ($n = 8$), 3–5 years ($n = 10$), 5–10 years ($n = 12$), 10–15 years ($n = 28$), and 15–20 years ($n = 16$). Accord-

ing to disease severity, the patients were divided into 4 subgroups: mild ($n = 12$), moderate ($n = 29$), severe ($n = 21$), and very severe ($n = 18$). The control group consisted of 20 healthy individuals. Patient inclusion criteria were informed consent to participate in the study and the presence of chronic eczema. Exclusion criteria included previous biological therapy, the presence of severe concomitant diseases or infectious pathology, and the use of systemic corticosteroids within 6 months prior to the start of the study.

The severity of eczema in patients was assessed using the Eczema Area and Severity Index (EASI), a validated clinical tool that evaluates four key signs of eczema: erythema, edema/papulation, excoriation, and lichenification across four body regions. The EASI provides a numerical score ranging from 0 (clear skin) to 72 (very severe eczema). For interpretation, a score of 0 indicates clear skin; 0.1–1.0, almost clear; 1.1–7.0, mild; 7.1–21.0, moderate; 21.1–50.0, severe; and 50.1–72.0, very severe eczema [11].

The expression of TLR2 and TLR4 was assessed by flow cytometry using monoclonal antibodies. The study was conducted in the immunology laboratory of the inter-institutional reference laboratory center of the National Academy of Medical Sciences of Ukraine. For detection, monoclonal antibodies against TLR2 conjugated with phycoerythrin (PE) (eBioscience, clone CI $\pm$ IA) and monoclonal antibodies against TLR4 conjugated with PE (eBioscience, clone Su-5, CIIIA) were used. Statistical analysis was performed using the Statistica software package.

RESULTS

As a result of the study, it was found that the age of patients with chronic eczema ranged from 24 to 81 years (mean age: 53.6 years). Most patients were aged 41–60 years (47.5%). Patients aged 24–40 years accounted for 20% of cases, whereas patients aged 61–81 years accounted for 32.5%.

The duration of chronic eczema varied widely, with the largest subgroup consisting of patients with disease duration of 10–15 years (18 patients; 35% of cases).

The course of chronic eczema was accompanied by pronounced skin dysbiosis involving both affected and unaffected skin, characterized by an increase in the total number of microorganisms (during relapse – 75.2 ± 0.9 CFU/cm² on affected skin and 28.1 ± 0.9 CFU/cm² on intact skin). During exacerbation, the microbial landscape was characterized by an increased colonization with *Enterococcus faecalis* (7.7 ± 0.9 CFU/cm²) and *Streptococcus pyogenes* (16.2 ± 1.3 CFU/cm²) on the affected skin, accompanied by a reduced concentration of Gram-positive flora (2.04 ± 0.13 CFU/cm²). During remission, Gram-negative bacteria were additionally identified,

together with an almost complete elimination of normal skin microbiota on unaffected skin.

In patients with chronic eczema, a significant increase in TLR2 expression was observed in men aged 61–81 years (118.00 ± 9.54 conventional units [CU]), particularly in patients with prolonged disease duration (15–20 years) and very severe eczema (EASI score: 50.1–72.0). In patients aged 24–40 years with disease duration below 3 years and mild eczema, epidermal TLR2 expression before treatment was lower than in patients aged 41–60 years with disease duration up to 10 years and moderate disease severity (table 1).

Although chronic eczema was more common in women, TLR2 expression levels were higher in men aged 61–81 years.

Analysis of TLR4 expression demonstrated elevated levels in both men and women aged 41–60 years, with

the most pronounced increase observed in men (approximately 2.04-fold higher compared with controls). After treatment, TLR4 expression decreased in both men and women. However, TLR4 levels remained at the upper limit of the reference range in men aged 41–60 years.

The duration of the disease (table 2) ranged from less than 1 year to 20 years. Disease duration of 10–15 years was observed in 28 patients (35%), 15–20 years in 16 patients (20%), 5–10 years in 12 patients (15%), 3–5 years in 10 patients (12.5%), 1–3 years in 8 patients (10%), and less than 1 year in 6 patients (7.5%).

Analysis of TLR expression according to disease duration demonstrated that TLR2 levels were highest in men with disease duration of 15–20 years, TLR4 expression was highest in men with disease duration of 3–5 years (5.02 ± 1.17 CU) and in women with the same disease duration (4.33 ± 1.37 CU).

Table 1. Changes in TLR2 and TLR4 expression levels measured by mean fluorescence intensity (MFI) in conventional units (CU) in patients with chronic eczema before and after treatment (study group, $n = 80$; control group, $n = 20$)

Group	Age group	Sex	TLR2 (CU)	TLR4 (CU)
Before treatment	24–40 years ($n = 16$)	M ($n = 6$)	74.05 ± 10.46	2.68 ± 0.24
		F ($n = 10$)	75.78 ± 6.83	2.38 ± 0.18
	41–60 ($n = 38$)	M ($n = 12$)	78.2 ± 4.80	4.92 ± 0.75
		F ($n = 26$)	79.71 ± 2.33	3.87 ± 0.25
	61–81 years ($n = 26$)	M ($n = 8$)	118.00 ± 9.54	3.14 ± 0.17
		F ($n = 18$)	82.88 ± 4.54	2.92 ± 0.08
After treatment	24–40 years ($n = 16$)	M ($n = 6$)	55.2 ± 8.61	2.65 ± 0.21
		F ($n = 10$)	56.2 ± 5.66	2.61 ± 0.13
	41–60 years ($n = 38$)	M ($n = 12$)	57.4 ± 3.92	3.52 ± 0.21
		F ($n = 26$)	59.2 ± 1.92	2.87 ± 0.09
	61–81 years ($n = 26$)	M ($n = 8$)	68.2 ± 8.32	2.79 ± 0.17
		F ($n = 18$)	69.4 ± 4.21	2.63 ± 0.09
Control group	24–40 years ($n = 20$)	M ($n = 10$)	53.6 ± 3.54	2.41 ± 0.06
		F ($n = 10$)	56.4 ± 3.75	2.81 ± 0.07
Reference values	Independent of age and sex		52.0–73.0	2.6–3.6

Data are presented as mean $\pm$ standard deviation. CU – conventional units.

Table 2. Changes in TLR2 and TLR4 expression levels measured by mean fluorescence intensity (MFI) in conventional units (CU) in patients with chronic eczema by disease duration

Duration of disease	Sex	TLR2 (CU)	TLR4 (CU)
< 1 year ($n = 6$)	M ($n = 2$)	68.88 ± 9.74	2.83 ± 0.33
	F ($n = 4$)	75.58 ± 4.48	2.84 ± 0.17
1–3 years ($n = 8$)	M ($n = 3$)	70.55 ± 8.65	2.73 ± 0.31
	F ($n = 5$)	75.77 ± 4.28	2.81 ± 0.16
3–5 years ($n = 10$)	M ($n = 8$)	78.68 ± 7.74	5.02 ± 1.17
	F ($n = 2$)	81.11 ± 10.37	4.33 ± 1.37
5–10 years ($n = 12$)	M ($n = 3$)	79.09 ± 8.75	4.63 ± 0.38
	F ($n = 9$)	81.04 ± 3.83	4.18 ± 0.14
10–15 years ($n = 28$)	M ($n = 2$)	84.64 ± 9.43	3.56 ± 0.26
	F ($n = 26$)	82.60 ± 1.54	3.20 ± 0.01
15–20 years ($n = 16$)	M ($n = 8$)	118.00 ± 9.54	3.14 ± 0.17
	F ($n = 8$)	75.21 ± 9.54	2.76 ± 0.17

Data are presented as mean $\pm$ standard deviation. CU – conventional units.

Table 3. TLR2 and TLR4 expression levels according to Eczema Area and Severity Index scores in patients with chronic eczema before treatment

EASI severity	Sex	TLR2 (CU)	TLR4 (CU)
1.1–7.0 – mild (<i>n</i> = 12)	M (<i>n</i> = 5)	69.88 ± 8.59	2.77 ± 0.15
	F (<i>n</i> = 7)	69.94 ± 6.04	2.95 ± 0.13
7.1–21.0 – moderate (<i>n</i> = 29)	M (<i>n</i> = 4)	77.41 ± 10.62	4.83 ± 1.76
	F (<i>n</i> = 25)	80.03 ± 2.84	3.50 ± 0.21
21.1–50.0 – severe (<i>n</i> = 21)	M (<i>n</i> = 9)	80.70 ± 7.69	4.65 ± 0.48
	F (<i>n</i> = 12)	80.15 ± 6.28	3.34 ± 0.36
50.1–72.0 – very severe (<i>n</i> = 18)	M (<i>n</i> = 8)	118.00 ± 9.54	3.14 ± 0.17
	F (<i>n</i> = 10)	86.99 ± 8.84	2.88 ± 0.16

Data are presented as mean ± standard deviation. CU – conventional units.

Evaluation of TLR expression according to EASI scores demonstrated that TLR2 expression was highest in men with very severe eczema (118.00 ± 9.54 CU; EASI score: 50.1–72.0), whereas TLR4 expression was highest in men and women with moderate disease severity (men: 4.83 ± 1.76 CU; women: 3.50 ± 0.21 CU) (table 3).

After therapy, TLR2 expression levels decreased significantly in all age groups and approached the levels observed in the control group. In men aged 41–60 years, TLR4 expression also decreased after treatment but remained at the upper limit of the reference range (table 1).

DISCUSSION

TLRs have an extracellular domain that recognizes pathogen-associated molecular patterns of microorganisms and an intracellular cytoplasmic domain involved in the induction of cellular immune responses [8]. Binding of microbial structures to the extracellular domain of TLRs initiates a cascade of intracellular signaling pathways involving key inflammatory mediators, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs). This activation results in the release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and chemokines such as interleukin-8 (IL-8/CXCL8), which contribute to the recruitment and activation of immune cells at the site of inflammation [12].

The innate immune system represents the first line of defense against invading pathogens. Following contact of microorganisms with the skin or mucous membranes, epithelial cells recognize microbial structures through TLRs and initiate the synthesis of inflammatory mediators and contribute to activation of adaptive immunity [13].

The results of recent studies indicate that microorganisms may represent an important aggravating factor in chronic eczema, and that activation of selected TLR subtypes contributes to the initiation and maintenance of inflammatory responses. Leung *et al.* re-

ported that endogenous TLR4 ligands mediate innate immune signaling and may induce or enhance allergic reactions [14]. Furthermore, some studies suggest that TLR4 signaling may regulate the development and severity of chronic eczema [15, 16]. Reduced interleukin-10 (IL-10) production associated with TLR4 signaling disturbances may contribute to the development of eczematous inflammation. Lin *et al.* demonstrated the immunoregulatory role of TLR4 signaling in a model of chronic eczema and reported more severe disease manifestations in TLR4-deficient models. Moreover, TLR4 signaling attenuated atopic dermatitis-like inflammation by inhibiting the migration of Langerhans-positive dendritic cells [17].

The findings of the present and previous studies demonstrate increased TLR2 expression in patients with prolonged disease duration and severe eczema, suggesting a possible association between TLR2 activation and persistent skin barrier dysfunction. Increased colonization with *Enterococcus faecalis* and *Streptococcus pyogenes* may additionally contribute to sustained activation of innate immune pathways [18].

Lower TLR2 expression observed in patients with shorter disease duration and milder eczema may indicate a less pronounced disruption of epidermal barrier function and reduced microbial colonization.

In the present study, TLR4 expression remained elevated in men aged 41–60 years even after the treatment, which may reflect persistent immune activation or ongoing skin barrier repair processes despite clinical improvement.

The results of this study are consistent with previously published data and complement current knowledge regarding changes in TLR2 and TLR4 expression in chronic eczema depending on disease duration, severity, and patient age.

CONCLUSIONS

TLR2 and TLR4 expression was associated with disease duration, eczema severity, and patient age in chronic eczema. A significant increase in TLR2

expression was observed in men aged 61–81 years during relapse of chronic eczema (118.00 ± 9.54 CU), associated with a prolonged disease duration (15–20 years). TLR4 expression was highest in men with disease duration of 3–5 years (5.02 ± 1.17 CU) and in women with the same duration (4.33 ± 1.37 CU), which may reflect activation of innate immune mechanisms associated with skin barrier restoration. Based on the EASI scores, the highest TLR2 expression was observed in patients with very severe eczema (EASI: 50.1–72.0), whereas the highest TLR4 expression was observed in patients with moderate disease severity (EASI: 7.1–21.0). Before treatment, TLR4 expression was elevated in both men and women aged 41–60 years, with the most pronounced increase observed in men (approximately 2.04-fold higher compared with controls). After treatment, TLR2 expression normalized across all groups. TLR4 expression decreased in most patients; however, in men aged 41–60 years it

remained at the upper limit of the reference range, which may indicate persistent immune activation or ongoing skin barrier repair processes.

FUNDING

No external funding.

ETHICAL APPROVAL

Protocol No. 22 of the meeting of the Committee on Ethics and Bioethics of the Kharkiv National Medical University dated October 3, 2024.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

1. Yang L., Fu J., Zhou Y.: Research progress in atopic march. *Front Immunol* 2020, 11, 1907.
2. Tokura Y., Yunoki M., Kondo S., Otsuka M.: What is "eczema"? *J Dermatol* 2025, 52, 192–203.
3. Afshari M., Kolackova M., Rosecka M., Čelakovská J., Krejssek J.: Unraveling the skin; a comprehensive review of atopic dermatitis, current understanding, and approaches. *Front Immunol* 2024, 15, 1361005.
4. Wollenberg A., Christen-Zäch S., Taieb A., Paul C., Thyssen J.P., de Bruin-Weller M., et al.: European Task Force on Atopic Dermatitis/EADV Eczema Task Force. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. *J Eur Acad Dermatol Venereol* 2020, 34, 2717–2744.
5. Ghafouri-Fard S., Abak A., Shoorai H., Talebi S.F., Mohaqiq M., Sarabi P., et al.: Interaction between non-coding RNAs and Toll-like receptors. *Biomed Pharmacother* 2021, 140, 111784.
6. Kawai T., Akira S.: Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011, 34, 637–650.
7. Fitzgerald K.A., Kagan J.C.: Toll-like receptors and the control of immunity. *Cell* 2020, 180, 1044–1066.
8. Duan T., Du Y., Xing C., Wang H.Y., Wang R.F.: Toll-like receptor signaling and its role in cell-mediated immunity. *Front Immunol* 2022, 13, 812774.
9. Weidinger S., Novak N., Klopp N., Ring J., Behrendt H., Illig T., et al.: Lack of association between Toll-like receptor 2 and Toll-like receptor 4 polymorphisms and atopic eczema. *J Allergy Clin Immunol* 2006, 118, 277–279.
10. Tamagawa-Mineoka R.: Toll-like receptors: their roles in pathomechanisms of atopic dermatitis. *Front Immunol* 2023, 14, 1239244.
11. Hanifin J.M., Baghoomian W., Grinich E., Leshem Y.A., Jacobson M., Simpson E.L.: The Eczema Area and Severity Index – a practical guide. *Dermatitis* 2022, 33, 187–192.
12. Majewska M., Szczepanik M.: Rola receptorów Toll-podobnych (TLR) w odporności wrodzonej i nabytej oraz ich funkcja w regulacji odpowiedzi immunologicznej [The role of Toll-like receptors (TLR) in innate and adaptive immune responses and their function in immune response regulation]. *Postepy Hig Med Dosw (Online)* 2006, 60, 52–63.
13. Ermertcan A.T., Öztürk F., Gündüz K.: Toll-like receptors and skin. *J Eur Acad Dermatol Venereol* 2011, 25, 997–1006.
14. Baioumy S.A., Taha S.I., Sallam D.E., Alashry A.I.A., Fouad S.H., Hegab M.A.: Toll-like receptor-4 gene (Asp299Gly) polymorphism in allergic conjunctivitis. *Egypt J Immunol* 2022, 29, 1–12.
15. Wang Y., Weng H., Song J.F., Deng Y.H., Li S., Liu H.B.: Activation of the HMGB1-TLR4-NF-κB pathway may occur in patients with atopic eczema. *Mol Med Rep* 2017, 16, 2714–2720.
16. Brandt E.B., Gibson A.M., Bass S., Rydzynski C., Khurana Hershey G.K.: Exacerbation of allergen-induced eczema in TLR4- and TRIF-deficient mice. *J Immunol* 2013, 191, 3519–3525.
17. Lin L., Xie M., Chen X., Yu Y., Liu Y., Lei K., et al.: Toll-like receptor 4 attenuates a murine model of atopic dermatitis through inhibition of langerin-positive DCs migration. *Exp Dermatol* 2018, 27, 1015–1022.
18. Dashchuk A., Mishyna M., Dashchuk A., Dobrzanska Y., Marchese A., Pisi R., et al.: Features of the skin microbiome in patients with chronic eczema during relapse. *Acta Biomed* 2026, 97, 18050.

Received: 15.01.2025

Accepted: 2.12.2025

Online publication: 30.04.2026

How to cite this article

Dashchuk A.A., Mishyna M.M., Dashchuk A.M., Dobrzanska Y.I.: Toll-Like Receptor Expression in Patients with Chronic Eczema. *Dermatol Rev/Przegl Dermatol* 2026, 113, 13–17. DOI: <https://doi.org/10.5114/dr.2026.162088>.