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Prevalence of the HLA-Cw6 genotype and zinc deficiency in psoriasis vulgaris patients in Indonesia

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Abstract

Introduction: Psoriasis vulgaris is an immune-mediated inflammatory disease influenced by genetic and immunologic factors, including micronutrient deficiencies. The HLA-Cw6 gene and zinc level have been separately studied in psoriasis patients, yielding inconsistent findings. A descriptive study regarding HLA-Cw6 allele expression, zinc levels, and their direct correlation in Indonesia is lacking.

Methods: This prospective case-control study involved 33 psoriasis patients and 33 age- and sex-matched control patients at the dermatology clinic affiliated with Hasanuddin University in South Sulawesi in 2021. Cases were classified into mild, moderate, and severe psoriasis according to Psoriasis Area and Severity Index (PASI) score. An EDTA tube was used to take a 5 ml blood sample, followed by analysis for PCR of the HLA-Cw6 allele and a colorimetric assay to measure zinc level. Statistical analysis was performed to determine the association between HLA-Cw6 and zinc level and psoriasis disease severity.

Results: Among the 33 psoriatic patients enrolled in this study, three (9.1%) of the cases were classified as mild psoriasis, 10 (30.3%) were classified as moderate psoriasis, and 20 (60.6%) were classified as severe psoriasis. The HLA-Cw6 allele was detected in 93.9% of psoriasis cases and in 3% of control patients ($p < 0.001$). The HLA-Cw6 allele was detected consecutively in 66.7%, 90.0%, and 100% of mild, moderate, and severe psoriasis patients, respectively. Zinc levels were lower in psoriasis patients compared to controls (16.85 ± 3.55 vs. 13.74 ± 3.78 µmol/l). Severe psoriasis patients exhibited the lowest average zinc level (14.76 ± 1.40 µmol/l, 15.48 ± 4.20 µmol/l, and 12.72 ± 3.56 µmol/l in mild, moderate, and severe patients, respectively). The mean zinc level in HLA-Cw6–positive patients was 13.68 µmol/l, and 14.6 µmol/l in HLA-Cw6–negative patients ($p = 0.495$).

Conclusions: The study revealed the presence of HLA-Cw6 allele expression and decreased serum zinc levels in psoriasis patients compared to controls. Both factors demonstrated associations with psoriasis disease severity.

Keywords: genetics, HLA-Cw6, micronutrient, psoriasis, serum level

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Introduction

Psoriasis is a polygenic disease; its manifestation is caused by the interaction of several genes. A strong genetic predisposition is known to be related to the major histocompatibility complex (MHC) gene. MHC signaling for psoriasis is HLA-C*0602 encoding for the *HLA-Cw6* gene. HLA-Cw6 presents the antigen on the surface of dendritic cells, which activate and drive CD8+ T cell proliferation. This process depends on CD4+ T cells, which play a role in the cross-presentation of intracellular antigens. CD4+ and CD8+ T cells are subsequently activated and proliferate. This cascade eventually leads to the differentiation of CD4+ T cells into key players such as Th17 cells, responsible for producing interleukins IL-17 and IL-22, central to psoriasis pathophysiology (1–2). Previous studies demonstrated HLA-Cw6 allele expression in 22% to 86% of psoriatic patients across various geographical locations (3–5). The HLA-Cw6 allele was associated with early onset of disease, a higher incidence of the Koebner phenomenon, more severe clinical presentation, and the occurrence of psoriatic arthritis (6).

Several micronutrients, including zinc, selenium, vitamin D, and omega 3, significantly influence disease progression. Zinc, a trace element vital to over 1,000 enzymatic processes, also exerts local antibacterial effects and supports innate immunity in the skin. Immunologically, it is indispensable for the differentiation, maturation, activation, and transduction of T-cell signaling (7). Notably, the skin is one of the organs with the highest zinc concentrations in the body. Keratinocyte hyperproliferation is the main pathophysiological feature in psoriasis, and zinc is needed for synthesis and nucleotide replication in cell proliferation (8). An analysis of 15 studies revealed a general trend of reduced serum zinc in psoriasis patients. However, the findings within these studies were inconclusive because some indicated decreased levels of serum zinc whereas others reported increased levels in patients with psoriasis. Moreover, zinc level in psoriasis patients is known to be related to the duration of the disease (7). Zinc is one of several nutrients known to ameliorate psoriasis (9). Published studies concerning zinc level, particularly in psoriasis patients in Indonesia, are currently lacking.

Given the polygenic and multifactorial nature of the disease, this study explores the prevalence of the HLA-Cw6 allele and plasma zinc level in psoriasis patients in South Sulawesi, Indonesia.

Methods

Research subjects and sampling

This prospective observational case-control study was conducted

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at the dermatology clinic of the hospital affiliated with Hasanuddin University in 2021. It enrolled patients with histopathologically confirmed psoriasis. Patients with incomplete data and those undergoing zinc supplementation were excluded from the study. Cases were consecutively selected until reaching the predefined minimum sample size. They were age- and sex-matched in a 1:1 ratio with control patients. Written informed consent was obtained from subjects 17 years and older, and written parental consent was obtained for subjects under 17. The study adhered to the ethical standards of the Declaration of Helsinki and was approved by the Ethical Committee of Hasanuddin University under reference number 345/UN4.6.4.5.31/PP36/2020.

Baseline characteristics

Age, sex, ethnicity, body weight, and body height were baseline characteristics assessed for each of the subjects. Body weight and body height were measured in the dermatology clinic during the first encounter using a calibrated weight scale and stadiometer. Body mass index (BMI) was calculated by dividing the weight in kg by the square of the height in meters. Participants self-reported their ethnicity based on paternal lineage.

Potential risk factors associated with psoriasis were evaluated through patient self-reports. These factors included stressful life events, intense sun exposure, smoking habits, diabetes status, and hypertension. Stressful life events were defined as significant undesirable occurrences leading to substantial life changes within 3 months prior to the onset of skin lesions. Intense sun exposure referred to occupational sun exposure or daily sun exposure exceeding 3 hours. Diabetes was classified based on physician diagnosis of type 1 or type 2 diabetes or the use of anti-diabetic medications. Similarly, hypertension was identified by physician diagnosis or the use of anti-hypertensive drugs.

Physical examinations and clinical assessments were performed by the authors to determine the Psoriasis Area and Severity Index (PASI) score. This score involved three components: thickness, scaling, and erythema, assessed for various body regions, including the head, upper extremities, trunk, and lower extremities. Each region received a score from 0 to 4. The scores for thickness, scaling, and erythema for each region were multiplied by the respective area involved and further multiplied by constants specific to each region. Summing up these scores provided a total PASI score ranging from 0 to 72. Disease severity classification was based on PASI scores: scores below 7 were considered mild, scores from 7 to 15 were categorized as moderate, and scores exceeding 15 were classified as severe (10–12). The assessment of disease severity was assessed by at least two authors.

DNA isolation

DNA was isolated from 3 ml of peripheral venous blood, 200 µl of whole blood sample was treated with EDTA by GoTaq® Green Master Mix (Promega Corp, catalog no. M 7122) following the manufacturer's instructions. A 200 µl sample was put into a 1.5 ml Eppendorf tube, and 20 µl of proteinase K and water were added until the volume reached 1 ml. The mix was incubated at 60 °C for 5 minutes.

HLA-Cw6 allelic analysis

Allele amplification was performed using an allele-specific primer (336 bp). The forward primer used was HLA-Cw6-F 5'-CCGAGTGAACCTGCGGAAA-3', and the reverse primer was HLA-Cw6-R 5'-GGTCGCAGCCATACATCCA-3'. PCR master mix was prepared using 12.5 µl GoTaq® Green, 0.5 µl forward primer, 0.5 µl reverse primer, 6.5 µl nuclease-free water, and 5.0 µl DNA sample with a total elution volume of 25 µl. PCR amplification was carried out using the BioRad iCycler iQ Thermal cycler (Bio-Rad, catalog no. 170-8740). The initial cycle involved pre-denaturation at 95 °C for 5 minutes. Subsequent cycles (40 in total) consisted of denaturation at 95 °C for 30 seconds, annealing at 50 °C for 30 seconds, and extension at 72 °C for 60 seconds. The final extension was conducted at 72 °C for 5 minutes.

Zinc colorimetric assay

A zinc colorimetric assay was performed using the Elabscience® Zinc colorimetric assay kit (catalog no. E-BC-K137-M) with analysis performed in the MR9600-AccuriSmartReader 96 Microplate Absorbance Reader (catalog no. 31-614E). A serum sample was prepared from 3 ml of peripheral venous blood. The blood was allowed to clot at 25 °C for 30 min. The resulting clot was centrifuged at 40 °C for 15 minutes at 2,000 *g*, and the upper yellowish clear liquid was collected. This sample was mixed with a protein precipitator at a 1:1 ratio and then centrifuged at 40 °C for 10 minutes at 13,780 g. The resulting supernatant was collected for detection. The standard well was prepared by diluting 1.54 µmol/l zinc standard solution with double distilled water to the recommended dilution gradient. Chromogenic agent solution was then added to both the sample and the standard wells. After shaking the microplate for 30 seconds, the mixture was allowed to stand for 5 minutes at room temperature. The optical density was measured at 560 nm using the microplate reader. The reference range for serum zinc concentration was set at 9.3 to 30.8 µmol/l (13).

Statistical analysis

Data were collected and analyzed using IBM® SPSS® version 25. Numerical baseline characteristics were presented as mean ± standard deviation for data exhibiting a normal distribution, and median ± interquartile range was employed for data showing an abnormal distribution. Categorical baseline characteristics were depicted as percentages relative to the total count. The association between HLA-Cw6 allele expression and psoriasis was analyzed using Fisher's exact test. Differences in zinc levels between cases and controls were analyzed using the Mann–Whitney test. Differences in zinc level among disease severity groups were analyzed using the Kruskal–Wallis test and multiple comparisons analysis for post hoc analysis. The association between HLA-Cw6 and zinc level was analyzed using the Mann–Whitney test.

Results

Baseline characteristic

Within the case group of 33 subjects (Table 1), three patients (9.1%) were classified as mild cases, 10 (30.3%) patients were classified as moderate, and 20 (60.6%) patients were classified as severe. There were 16 (48.5%) male and 17 (51.5%) female subjects, with homogenous age and ethnicity distribution among severity groups. The subjects' ages ranged from 13 to 72 years, with a mean age of 36.7 ± 15.2 years, consistently distributed across the severity groups. BMI exhibited significant variation among the severity

groups. Specifically, the mean BMI was 31.5 ± 4.0 kg/m² for mild psoriasis, 23.2 ± 3.0 kg/m² for moderate psoriasis, and 24.9 ± 4.2 kg/m² for severe psoriasis ($p = 0.011$).

Moreover, an array of risk factors and comorbidities was observed among the cases, with a notably higher prevalence within the moderate and severe psoriasis groups.

HLA-Cw6

As indicated in Table 2, HLA-Cw6 expression was detected in 31 patients (93.9%). In contrast, among the control patients, only one individual (3.0%) exhibited HLA-Cw6 alleles ($p < 0.001$). Among the psoriasis patients, HLA-Cw6 alleles were expressed in two out of three patients (66.7%) with mild psoriasis, nine out of 10 patients (90%) with moderate psoriasis, and all 20 patients (100%) with severe psoriasis.

Baseline characteristics were also analyzed according to HLA-Cw6 allele expression (Table 3). Both HLA-Cw6–negative cases were male. The mean age among HLA-Cw6–positive cases was 35.68 ± 15.08 years, and in HLA-Cw6–negative cases it was 53.00 ± 8.40 years.

Zinc

Zinc levels (Table 4) were notably lower in psoriasis patients in comparison to the control group (13.74 ± 3.78 µmol/l in psoriasis vs. 16.85 ± 3.55 µmol/l in control). Among psoriasis patients (Table 5), those with severe symptoms exhibited the lowest average zinc levels (14.76 ± 1.40 µmol/l, 15.48 ± 4.20 µmol/l, and 12.72 ± 3.56 µmol/l for mild, moderate, and severe cases, respectively).

Multiple comparisons analysis among groups (Tables 6 and 7) showed a statistically significant difference between severe psoriasis and the control group, with a mean difference of 4.13 ± 1.02 ($p = 0.000$).

In addition, Table 8 shows the correlation between disease duration and zinc levels. A very weak negative correlation between disease duration and zinc levels is observed.

Table 1 | Baseline patient characteristics by psoriasis severity.

Parameter	Psoriasis severity			Control
	Mild	Moderate	Severe	
Total, *n*	3	10	20	33
Males, *n* (%)	1 (33.3)	4 (40.0)	11 (55.0)	16 (48.4)
Ethnicity				
Bugis	2	5	7	15
Makassar	1	5	12	17
Duri	0	0	1	0
Betawi	0	0	0	1
Age (years), mean ± *SD*	44.0 ± 7.9	36.3 ± 18.2	35.9 ± 14.8	36.7 ± 15.3
BMI (kg/m²), mean ± *SD*	31.5 ± 4.0	23.2 ± 3.0	24.9 ± 4.2	21.0 ± 1.5
Disease duration (months), mean ± *SD*	24.0 ± 21.0	17.2 ± 17.7	11.4 ± 13.5	—
Risk factors (*n*, %)				
Stress	0	8 (80.0)	13 (65.0)	—
Sun exposure	0	0	1 (5.0)	
Smoking	1 (33.3)	0	2 (10.0)	
Diabetes	0	1 (10.0)	0	
Hypertension	0	1 (10.0)	2 (10.0)	

BMI = body mass index, *SD* = standard deviation.

Table 2 | HLA-Cw6 allele expression by psoriasis severity.

HLA-Cw6 allele	Psoriasis severity			Total
	Mild	Moderate	Severe	
Expressed (*n*, %)	2, 66.7	9, 90.0	20, 100.0	31, 93.9
Not expressed (*n*, %)	1, 33.3	1, 10.0	0, 0.0	2, 6.1
Total (*n*, %)	3, 100.0	10, 100.0	20, 100.0	33, 100.0

Table 3 | Baseline patient characteristics by HLA-Cw6 allele expression.

Parameter	HLA-Cw6	
	Positive	Negative
Total (*n*)	31	2
Sex, male (*n*, %)	14 (45.16)	2 (100.00)
Age (years), mean ± *SD*	35.68 ± 15.08	53.00 ± 8.48
Risk factors (*n*, %)		
Smoking	2 (6.5)	1 (50.0)
Metabolic disease	4 (12.9)	0 (0)
Stress	22 (70.9)	1 (50.0)
Sun exposure	1 (3.2)	0 (0)

SD = standard deviation.

Table 4 | Serum zinc level difference (µmol/l) between cases and controls, Mann–Whitney test.

Group	*n*	Mean	SD	Mean difference (95% CI)	*p*
Cases	33	13.74	3.78	3.11 (1.30–4.91)	< 0.001
Controls	33	16.85	3.55		

SD = standard deviation, CI = confidence interval.
Reference range for serum zinc 9.3–30.8 µmol/l.

Table 5 | Comparison of serum zinc level (µmol/l) by psoriasis disease severity.

Disease severity	*n*	Mean	*SD*	*p*
Mild	3	14.76	1.40	
Moderate	10	15.48	4.20	
Severe	20	12.72	3.56	0.001
Control	33	16.85	3.55	

SD = standard deviation.
Reference range for serum zinc 9.3–30.8 µmol/l.

Table 6 | Multiple comparisons of zinc levels among different sample groups.

(I) Sample groups	(J) Sample groups	Mean difference (I – J)	Std. error	*p*	95% CI	
					Lower bound	Upper bound
Mild	Moderate	−0.72	2.37	0.763	−5.46	4.03
	Severe	2.03	2.23	0.366	−2.43	6.50
	Control	−2.09	2.17	0.340	−6.44	2.25
Moderate	Mild	0.72	2.37	0.763	−4.03	5.46
	Severe	2.75	1.40	0.053	−0.04	5.54
	Control	−1.37	1.30	0.295	−3.98	1.23
Severe	Mild	−2.03	2.23	0.366	−6.50	2.43
	Moderate	−2.75	1.40	0.053	−5.54	0.04
	Control	−4.13*	1.02	0.000	−6.17	−2.08
Control	Mild	2.09	2.17	0.340	−2.25	6.44
	Moderate	1.37	1.30	0.295	−1.23	3.98
	Severe	4.13*	1.02	0.000	2.08	6.17

CI = confidence interval.
Measurement unit µmol/l.
*mean difference significant at 0.05.

Table 7 | **Correlation between Psoriasis Area and Severity Index (PASI) score and zinc level.**

	PASI score	Zinc level
PASI score	1	−0.395*
Zinc level	−0.395*	1

Spearman correlation.
*correlation significant at 0.05.

Table 8 | **Correlation between disease duration and zinc level.**

	Disease duration	Zinc level
Disease duration	1	−0.164
Zinc level	−0.164	1

Spearman correlation.

HLA-Cw6 and zinc level

The mean zinc level in patients that were positive for the HLA-Cw6 allele was 13.68 µmol/l, whereas it was 14.6 µmol/l in HLA-Cw6–negative patients (p = 0.495; Table 9).

Table 9 | **Serum zinc level (µmol/l) by HLA-Cw6 expression.**

Groups	HLA-Cw6 allele	*n*	Mean	*SD*	*p*
Cases	Positive	31	13.68	3.89	0.495
	Negative	2	14.67	0.93	
Control	Positive	1	18.63		—
	Negative	32	16.79	3.59	

SD = standard deviation.

Discussion

In this study, HLA-Cw6 allele expression was found in 93.9% of cases. Notably, across the Asian population, HLA-Cw6 positivity among psoriasis patients has been reported at levels as low as 10.5% to 12.0% in Japan (14–16) and as high as 17.9% to 29.8% in India (17–19). A review by Chen et al. stated that the prevalence of the HLA-Cw6 allele in the general population varies from 14.1% to 59.1%, whereas among psoriasis patients it ranges from 10.5% to 77.2% (20). In the Indonesian population, an HLA-Cw6 positivity rate of 22% was observed in psoriasis patients with Javanese ethnicity (3). Interestingly, a study by Amr et al. showed HLA allele expression in 86% of psoriasis patients in the Egyptian population (4). Notably, the HLA-Cw6 expression rate found in this study surpasses that of other studies conducted in various geographical areas. This disparity may stem from ethnic distinctions or selection bias, potentially linked to the study's setting in a tertiary healthcare center where a considerable proportion of patients exhibited severe psoriasis. Intriguingly, the severe psoriasis group in this study demonstrated 100% expression of HLA-Cw6 alleles. It is important to highlight that this study marks the first exploration of HLA-Cw6 allele prevalence among psoriasis patients in eastern Indonesia.

The prevalence of the HLA-Cw6 allele varies across psoriasis severity categories: 66.7% in mild cases, 90% in moderate cases, and a full 100% in severe psoriasis patients. Interestingly, individuals positive for the HLA-Cw6 allele tend to exhibit a younger mean age. The impact of HLA-Cw6 on the clinical presentation of psoriasis is well documented. A study by Gudjonsson et al. found that patients with the HLA-Cw6 allele experience earlier disease onset, increased lesion count, more severe disease manifestations, and a heightened incidence of the Koebner phenomenon (21). This allele's influence on psoriasis phenotype extends to the Indonesian population, where HLA-Cw6 has been identified as a genetic risk factor for severe psoriasis (22).

The presence of the HLA-Cw6 allele was detected in one patient without the disease, a 28-year-old male. This observation concurs with research from Japan and South Korea, which has shown HLA-Cw6 positivity in controls ranging from 0% to 8.1% (14–16, 23). A study by Amr et al. found HLA-Cw6 allele positivity in 40% of controls in the Egyptian population (4, 18). In a study by Chandra et al. in 2016, some of the controls eventually develop late-onset psoriasis after age 40 (18). HLA-Cw6 is a major susceptibility gene in psoriasis; however, the gene penetrance is only 10%, and interaction with other susceptibility genes is required for the psoriasis phenotype to occur (1).

Zinc, an essential trace element, plays a critical role in protein synthesis, RNA and DNA repair, enzymatic activity regulation, and scavenging of free radicals. Zinc influences psoriasis disease activity by regulating keratinization, immunological, and enzymatic function. In this study, the mean zinc level in patients was lower than in the control group. Four patients had zinc levels below the laboratory's reference range, one with moderate psoriasis and three with severe psoriasis, whereas no patients in the control group had serum zinc levels below the reference range in this study. Moreover, a weak negative correlation was observed between the PASI score and zinc level in psoriasis patients in this study. The mean difference of serum zinc in severe psoriasis compared to control was −4.13 (p < 0.05), above the test's detection limit. In a study by Al-Jebory et al., 98% of the subjects were found to be zinc deficient (cutoff 12–17 µmol/l), with serum zinc in the psoriasis group ranging from 10.01 to 13.81 µmol/l and a mean serum level of 11.25 ± 0.84 µmol/l, which is slightly lower compared to our study (24). Despite previous studies demonstrating varying results concerning serum zinc levels in psoriasis patients, a meta-analysis of 15 studies indicated a significantly reduced serum zinc level in psoriasis patients (7). Although not statistically significant, HLA-Cw6–positive cases had lower mean serum zinc levels compared to the HLA-Cw6–negative group. This observation could potentially be attributed to a propensity for more severe disease among HLA-Cw6–positive cases. It is noteworthy that the skin, as the organ with the highest zinc concentration in the body, undergoes excess keratinocyte proliferation in psoriasis, leading to increased zinc consumption and subsequent serum zinc deficiency (25).

Conclusions

This study revealed that HLA-Cw6 allele expression was present in 93.9% of psoriasis patients, rising to 100% in those with severe psoriasis. Psoriasis patients displayed reduced serum zinc levels compared to the control group, with a particularly pronounced discrepancy observed between severe psoriasis patients and controls. Furthermore, HLA-Cw6–positive cases exhibited lower serum zinc levels in comparison to HLA-Cw6–negative cases. Based on these findings, we recommend considering routine assessments of HLA-Cw6 allele status and zinc levels for newly diagnosed psoriasis vulgaris patients.

References

1. Gudjonsson JE, Elder JT. Psoriasis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. Fitzpatrick's dermatology. 9th ed. New York: McGraw-Hill Education; 2019. p. 1727.
2. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol. 2017;76: 377–90.
3. Sylviningrum T, Putranti IO, Sari OP, Arjadi F, Sudibyo ES, Manik SN. Association between HLA-Cw6 allele expression and characteristics of Javanese ethnic psoriasis patients in Indonesia. Med J Indones. 2019;28:370–4.
4. Amr K, Weshahy A, El Hadidi FM, El Hamid A, Oteafy M, Aly D. A pilot study of HLA-Cw6 association with Egyptian psoriatic patients. Res J Med Med Sci. 2010; 5:25–9.
5. Atasoy M, Pirim I, Bayrak O, Ozdemir S, Ikbal M, Erdem T, et al. Association of HLA class I and class II alleles with psoriasis vulgaris in Turkish population. Audi Med J. 2006;27:373–6.
6. Muñoz-Aceituno E, Martos-Cabrera L, Ovejero-Benito MC, Reolid A, Abad-Santos F, Daudén E. Pharmacogenetics update on biologic therapy in psoriasis. Medicina. 2020;56:719.
7. Lei L, Su J, Chen J, Chen W, Chen X, Peng C. Abnormal serum copper and zinc levels in patients with psoriasis: a meta-analysis. Indian J Dermatol. 2019;64:224–30.
8. Chen W, Zhou X, Zhu W. Trace elements homeostatic imbalance in psoriasis: a meta-analysis. Biol Trace Elem Res. 2019;191:313–22.
9. Kanda N, Hoashi T, Saeki H. Nutrition and psoriasis. Int J Mol Sci. 2020;21:5405.
10. Oji V, Luger TA. The skin in psoriasis: assessment and challenges. Clin Exp Rheumatol. 2015;33:S14–9.
11. Burden AD, Kirby B. Psoriasis and related disorders. In: Griffiths CEM, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's textbook of dermatology 2. 9th ed. Oxford: John Wiley & Sons; 2016. p. 1133–80.
12. Llamas-Velasco M, De la Cueva P, Notario J, Martínez-Pilar L, Martorell A, Moreno-Ramírez D. Moderate psoriasis: a proposed definition. Actas Dermosifiliogr. 2017;108:911–7.
13. Ghasemi A, Zahediasl S, Hossein-Esfahani F, Azizi F. Reference values for serum zinc concentration and prevalence of zinc deficiency in adult Iranian subjects. Biol Trace Elem Res. 2012;149:307–14.
14. Asahina A, Akazaki S, Nakagawa H, Kuwata S, Tokunaga K, Ishibashi Y, et al. The specific nucleotide sequence of HLA-C is strongly associated with psoriasis vulgaris. J Invest Dermatol. 1991;97:254–8
15. Nakagawa H, Asahina A, Akazaki S, Tokunaga K, Matsuki K, Ishibashi Y, et al. Association of Cw11 in Japanese patients with psoriasis vulgaris. Tissue Antigens. 1990;36:241–2.
16. Oka A, Tamiya G, Tomizawa M, Ota M, Katsuyama Y, Makino S, et al. Association analysis using refined microsatellite markers localizes a susceptibility locus for psoriasis vulgaris within a 111 kb segment telomeric to the HLA-C gene. Hum Mol Genet. 1999;8:2165–70.
17. Rani R, Narayan R, Femandez-Vina M, Stastny P. Role of HLA-B and C alleles in development of psoriasis in patients from North India. Tissue Antigens. 1998; 51:618–22.
18. Chandra A, Lahiri A, Senapati S, Basu B, Ghosh S, Mukhopadhyay I, et al. Increased risk of psoriasis due to the combined effect of HLA-Cw6 and LCE3 risk alleles in the Indian population. Sci Rep. 2016;6:24059.
19. Indhumathi S, Rajappa M, Chandrashekar L, Ananthanarayanan P, Thappa D, Negi V. The HLA-C* 06 alleles as a possible genetic predisposing factor to psoriasis in South Indian Tamils. Arch Dermatol Res. 2016;308:193–9.
20. Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018;178:854–62.
21. Guðjónsson JE, Valdimarsson H, Kárason A, Antonsdóttir AA, Rúnarsdóttir EH, Gulcher JR, et al. HLA-Cw6-positive and HLA-Cw6-negative patients with psoriasis vulgaris have distinct clinical features. J Invest Dermatol. 2002;118:362–5.
22. Sri Lestari KS, Darwin E, Jacoeb TNA, Tjong DH. The relationship between human leukocyte antigen-Cw6 allele and psoriasis vulgaris. Dermatol Reports. 2019;11.
23. Kim TG, Han H, Lee HJ, Youn JI, Kim TY. The association of psoriasis with human leukocyte antigens in the Korean population and the influence of age of onset and sex. J Invest Dermatol. 2000;114:309–13.
24. Al-Jebory A. Serum zinc in psoriatic patients. Mustansiriya Med J. 2012;11:20–3.
25. Sheikh G, Masood Q, Majeed S, Hassan I. Comparison of levels of serum copper, zinc, albumin, globulin, and alkaline phosphatase in psoriatic patients and controls: a hospital-based case-control study. Indian Dermatol Online J. 2015;6:81.