Original Article

Correlation between Psoriasis and ZIP2 and ZIP3 Zinc Transporters

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Abstract

Aims: Psoriasis is a chronic, inflammatory, hyperproliferative skin disease with etiopathogenesis not fully understood. The zinc transporter ZIP2 is associated with keratinocyte differentiation, whereas ZIP3 is associated with T-lymphocyte maturation. In our study, we aimed to show the correlation between psoriasis and ZIP2 and ZIP3 zinc transporters in psoriasis patients. **Subjects and Methods:** The patient group in the study included 60 patients aged with psoriasis vulgaris and a control group of 60 healthy adults. The levels of ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporters were determined with the ELISA method. Results were compared with control group values and statistically assessed. **Results:** When the ZIP2 and ZIP3 levels are compared in controls and psoriasis patients, the levels were observed to significantly increase compared to controls ($P < 0.05$). When compared to the control group, the results appeared to be statistically significant ($P < 0.05$). **Conclusions:** With etiopathogenesis not fully known, there may be an important relationship between psoriasis development and ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporters in psoriasis vulgaris patients. This situation may be an important result for understanding how the disease develops and in creating new approaches in terms of treatment for this disease without full cure available.

Keywords: Psoriasis vulgaris, zinc transporters, ZIP2 (SLC39A2), ZIP3 (SLC39A3)

Introduction

Psoriasis is a chronic, systemic, inflammatory, and hyperproliferative skin disease observed at 2%–3% incidence. The most commonly observed clinical type is plaque-type psoriasis (psoriasis vulgaris), and lesions are localized to the scalp, extensor surfaces of the extremities, and sacrogluteal regions, characterized by erythematous squamous plaques with definite margins. Although the etiopathogenesis is still uncertain, it is accepted that cytokines such as interleukin (IL)-17, IL-23, and tumor necrosis factor-alpha (TNF-α) play important roles in the development of psoriasis. The IL-23 and TNF-α produced by inflammatory dendritic cells in the skin induce IL-17 production from Th17 or γδT cells in the skin, and IL-17 is thought to basically affect keratinocytes beginning dermatitis.[1]

Zinc is an important trace element. Severe zinc deficiency is associated with skin diseases and lack of regular operation of the immune system. Most zinc stores in the body are found linked to metalloproteins within cells. Zinc homeostasis is tightly controlled by zinc transporters. Of zinc transporters, ZIP2 is especially associated with keratinocyte differentiation, whereas ZIP3 is associated with T-lymphocyte maturation.[2,3]

In psoriasis patients, studies assessing serum zinc levels have obtained contradictory results. No amelioration is observed in lesions even with zinc supplementation administered to psoriasis patients with low serum zinc levels.[4-6] This situation leads to the consideration that psoriasis pathogenesis may be related not to systemic zinc deficiency but to deficiency at cellular level related to erroneous cutaneous zinc input. The aim of our study, based on literature data, is to assess the levels of zinc transporters providing zinc input into cells, which we consider to have an important role in etiopathogenesis in psoriasis patients and to research the correlation with psoriasis development.

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Subjects and Methods

Study design and patients

Our study was permitted by Çanakkale Onsekiz Mart University (ÇOMÜ) Rectorate Clinical Research Ethics Committee on July 11, 2018, number 13-08. It was supported by ÇOMÜ Scientific Research Commission with an independent research project coded THD-2018-2669. Our study group comprised patients attending our clinic from September 2018 to October 2019. The study included 60 psoriasis vulgaris patients aged 18 years and older monitored for at least 2–3-month periods and a control group of 60 healthy adults aged 18 years and older. The control group had no psoriasis lesions on dermatologic examination, had no other systemic disease and/or no systemic medication use, and comprised randomly chosen healthy adults. Before the study, each participant was informed about the aim of the study and written consent was obtained. Blood was centrifuged, and then, serum samples were stored until analysis at −80°C in a freezer.

Laboratory parameters

ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporter levels were determined with the ELISA method using suitable commercial kits (ZIP2-MBS9331175 and ZIP3-MBS927886; MyBioSource, San Diego, CA, USA). After collecting data, statistical analyses were completed and significance analysis was performed for the control and study groups.

The ZIP2 and ZIP3 analyses were completed with the quantitative sandwich ELISA method. Microplate, standards, and samples were brought to room temperature (18°C–25°C). The blind well had no chemical added. After standards and samples were pipetted into the wells, horseradish peroxidase-conjugated reagent was added and was incubated at 37°C for 60 min. All wells were washed four times. Then, each well had chromogen A and B solutions added and was incubated at 37°C for 15 min, and then, the reaction was stopped with stop solution. Optical intensity was measured at 450 nm within 15 min of adding the stop solution. Based on the graphs obtained from standards, concentrations of samples were determined.

Statistical analysis

Statistical analysis of ZIP2 and ZIP3 levels in the psoriasis and control groups was completed using the IBM SPSS statistics 21.0 program (Chicago, IL, USA). Statistical significance was accepted as $P < 0.05$. Differences between groups were determined with the Kolmogorov-Smirnov ($P < 0.05$) and nonparametric Mann–Whitney U-test for ZIP2 ($P = 0.000$). For ZIP3, groups had normal distribution according to the Kolmogorov-Smirnov test ($P > 0.05$), so the independent *t*-test was applied ($P < 0.05$). Correlations between demographic data and ZIP2 and ZIP3 values were determined with the Pearson and Spearman correlation tests. Results are expressed as mean ± standard deviation.

Results

When the ZIP2 levels are compared in controls and psoriasis patients, they appear to increase by significant levels compared to controls ($P < 0.05$) [Figure 1 and Table 1]. At the same time, the ZIP3 levels were increased in psoriasis, similar to ZIP2 [Figure 1 and Table 1]. When assessed compared to the control group, the results are statistically significant ($P < 0.05$).

Discussion

Zinc is categorized as a trace element comprising <0.005% of total body weight. In circulation, it is found at concentrations of 70–120 mcg/dL, with 60% linked to albumin and 30% linked to macroglobulin. Primary zinc stores are the liver and kidneys. However, body zinc stores are found linked to metalloproteins in most cells. It is a natural metal compound or activating cofactor for more than 70 important enzyme systems, led by alkaline phosphatase. It plays a role in regulation of nucleoproteins and inflammatory cell activation.[7]

Zinc is very important for the immune system. Phagocytic function disorder resulting from zinc deficiency is associated with lymphocyte reduction, reduced immunoglobulin production, reduced T4/T8 ratio, and reduced IL-2 production.[8] The interaction between T-lymphocytes and IL-2 is important for both tolerance and immune response. When literature data are investigated, increases in IL-2 appear to be associated with a reduction in psoriasis severity and an increase in quality of life.[9,10] The role of IL-2 in psoriasis is to ensure differentiation of regulatory T-cells from immature T-cells and to ease differentiation of infector and memory cells in T-cells exposed to antigens. In addition, it is debatable whether the reduction in IL-2 levels is associated with psoriasis development or not.[11,12]

ZIP2 is a zinc transporter found in cell membranes and plays a role in zinc intake into cells. It is found at higher levels in the epidermis than the dermis. In psoriasis, epidermal turnover is shorter by eight times compared to normal and keratinocyte differentiation remains insufficient. ZIP2 is required for both proliferation and terminal differentiation of keratinocytes in epidermal turnover, and a study showed ZIP2 levels increased in parallel with differentiation.[2,13] Keratinocytes increase ZIP 2 expression when extracellular zinc levels are reduced, thereby maintaining homeostasis and preserving the ability to differentiate. A similar phenomenon was observed in a study using monocytic cells.[14] Another study observed vesiculobullous lesions formed on the skin during early embryogenesis in ZIP2 knockout mice,[15] and although the underlying mechanism is not fully known, this situation is probably due to abnormal differentiation of keratinocytes.

ZIP3 is expressed at high rates by CD34+ human hematopoietic stem cells, and a study of mice showed a correlation between ZIP3

Table 1: Comparison of ZIP2 and ZIP3 levels in the psoriasis and control groups

	ZIP2	ZIP3
Control	1.69±1.42*	109.61±70.88*
Psoriasis	8.39±5.51[b]	965.06±698.54[b]

Results shown with [b]are seen to be statistically significant when compared with those marked *$P<0.05$

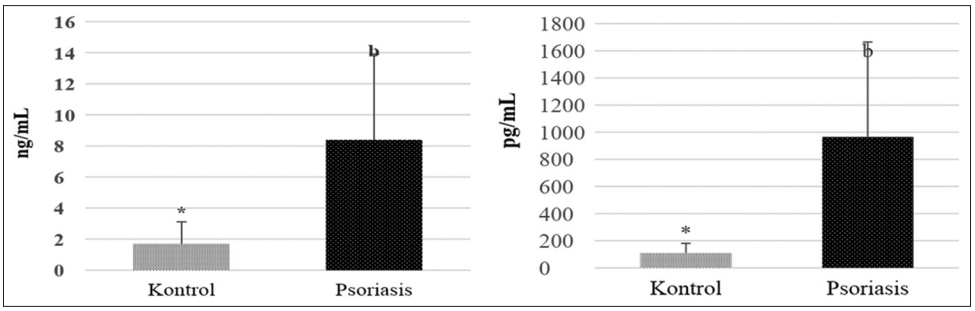

Figure 1: ZIP2 (SLC39A2) and ZIP3 (SLC39A3) zinc transporter levels in psoriasis patients

and T-cell maturation.[3] Psoriasis is a T-lymphocyte-mediated disease and is thought to occur as a result of complex mechanisms between T-lymphocytes with dendritic cells, macrophages, mast cells, neutrophils, and keratinocytes.

Cutaneous changes are frequently observed in patients with zinc deficiency. Acrodermatitis enteropathica is a rare disease forming as a result of a hereditary partial defect in intestinal zinc absorption with recessive transition. The disease was identified to cause mutation in the gene for the zinc transporter protein ZIP4 (SLC39A4).[16] In affected infants, as a result of zinc deficiency, there is skin involvement with appearance of erythematous and vesiculobullous lesions and alopecia with clinical findings affecting other systems such as growth development retardation, delayed sexual maturation, neuropsychiatric symptoms, and frequent infections. The syndrome responds to oral zinc supplementation.

When studies about the serum zinc levels in psoriasis patients are investigated, there are contradictory results reported. Some researchers have found low serum zinc levels in psoriasis patients compared to the control group,[17,18] whereas some have not found such a difference.[19,20] In psoriasis patients, a study comparing epidermal and serum zinc levels found that epidermal and serum zinc levels were not correlated; however, epidermal zinc values were lower in psoriasis patients.[21] This result shows that patients with reduced epidermal zinc concentrations may have zinc deficiency even if they have normal serum zinc values. In addition, in psoriasis patients, even with low serum zinc concentrations, oral zinc supplements remain as effective as placebo.[5] As a result, in relation to psoriasis development, it may be considered a defect of subcellular zinc metabolism caused by erroneous zinc input into the skin rather than systemic zinc deficiency. In our study, we found that ZIP2 and ZIP3 levels were higher in our psoriasis patients independent of disease severity. This situation leads us to consider it may form as a result of complicated correlations between disrupted zinc homeostasis, increased keratinocyte proliferation, and chronic inflammatory cell infiltration.

Conclusions

For immune-mediated diseases such as psoriasis, there is still no treatment method providing full cure or no laboratory test assessing disease severity or treatment efficacy.[22] In addition, the effect of the most effective treatments sometimes reduces due to changes in cytokine profile and may even become ineffective. In conclusion, the increase in ZIP2 and ZIP3 levels obtained in our psoriasis patients may be a marker of a zinc deficiency at cellular level in accordance with roles in pathogenesis. Zinc deficiency at cellular level affects the cytokine profile, and we think that zinc deficiency at the cellular level affects the cytokine profile. This may be important in the pathogenesis of psoriasis lesions. It may even explain why psoriasis patients have different treatment responses to similar treatments.

The importance of the zinc carrier family is emphasized by the numerous functions of these proteins in many disease states. Irregularity of zinc transporters causes dissociation in intracellular zinc levels. this situation have profound effects on metabolic homeostasis, which affects multiple signaling pathways associated with normal development, growth, differentiation, and death. Zinc carriers are essential for the control of intracellular zinc. Mechanisms that disrupt this process may contribute to the development of psoriasis, one of the inflammatory and chronic inflammatory diseases. Targeting these zinc carriers in psoriasis therapy can lead to the development of new treatment options.[23]

In light of our data, we think that zinc transporters may be assessed as a part of treatment of psoriasis patients, perhaps to optimize treatments.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017;140:645-53.

2. Rezaei KA, Chen Y, Cai J, Sternberg P. Modulation of Nrf2-dependent antioxidant functions in the RPE by Zip2, a zinc transporter protein. Invest Ophthalmol Vis Sci 2008;49:1665-70.
3. Dufner-Beattie J, Huang ZL, Geiser J, Xu W, Andrews GK. Generation and characterization of mice lacking the zinc uptake transporter ZIP3. Mol Cell Biol 2005;25:5607-15.
4. Verma S, Thakur BK. Dramatic response to oral zinc in a case of subacute form of generalized pustular psoriasis. Indian J Dermatol 2012;57:323-4.
5. Voorhees JJ, Chakrabarti SG, Botero F, Miedler L, Harrell ER. Zinc therapy and distribution in psoriasis. Arch Dermatol 1969;100:669-73.
6. 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.
7. Beyersmann D, Haase H. Functions of zinc in signaling, proliferation and differentiation of mammalian cells. Biometals 2001;14:331-41.
8. Prasad AS. Zinc and immunity. Mol Cell Biochem 1998;188:63-9.
9. Khandpur S, Gupta V, Das D, Sharma A. Is there a correlation of serum and tissue T helper-1 and -2 cytokine profiles with psoriasis activity and severity? A cross-sectional study. Indian J Dermatol Venereol Leprol 2018;84:414-8.
10. Solberg SM, Sandvik LF, Eidsheim M, Jonsson R, Bryceson YT, Appel S. Serum cytokine measurements and biological therapy of psoriasis – Prospects for personalized treatment? Scand J Immunol 2018;88:e12725.
11. Adler G, Skonieczna-Żydecka K, Madlani A, Ogonowski J, Grochans E, Pierzak-Sominka J, *et al*. Association between depression, parameters of adiposity and genetic polymorphisms of pro-inflammatory cytokines: IL-1α, IL-1β, IL-2 and IL-6 in subjects over 55 years old. Acta Biochim Pol 2016;63:253-9.
12. Tucker P, Pfefferbaum B, Nitiéma P, Khan Q, Aggarwal R, Walling EE. Possible link of Interleukin-6 and Interleukin-2 with psychiatric diagnosis, ethnicity, disaster or BMI. Cytokine 2017;96:247-52.
13. Inoue Y, Hasegawa S, Ban S, Yamada T, Date Y, Mizutani H, *et al*. ZIP2 protein, a zinc transporter, is associated with keratinocyte differentiation. J Biol Chem 2014;289:21451-62.
14. Cao J, Bobo JA, Liuzzi JP, Cousins RJ. Effects of intracellular zinc depletion on metallothionein and ZIP2 transporter expression and apoptosis. J Leukoc Biol 2001;70:559-66.
15. Peters JL, Dufner-Beattie J, Xu W, Geiser J, Lahner B, Salt DE, *et al*. Targeting of the mouse Slc39a2 (Zip2) gene reveals highly cell-specific patterns of expression, and unique functions in zinc, iron, and calcium homeostasis. Genesis 2007;45:339-52.
16. Küry S, Dréno B, Bézieau S, Giraudet S, Kharfi M, Kamoun R, *et al*. Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. Nat Genet 2002;31:239-40.
17. Morgan ME, Hughes MA, McMillan EM, King I, Mackie RM. Plasma zinc in psoriatic inpatients treated with local zinc application. Br J Dermatol 1980;102:579-83.
18. Greaves M, Boyde TR. Plasma-zinc concentrations in patients with psoriasis, other dermatoses, and venous leg ulceration. Lancet 1967;2:1019-20.
19. Molokhıa MM, Portnoy B. Neutron activation analysis of trace elements in skin V. Copper and zinc in psoriasis. Br J Dermatol 1970;83:376-81.
20. Hinks LJ, Young S, Clayton B. Trace element status in eczema and psoriasis. Clin Exp Dermatol 1987;12:93-7.
21. Michaëlsson G, Ljunghall K. Patients with dermatitis herpetiformis, acne, psoriasis and Darier's disease have low epidermal zinc concentrations. Acta Derm Venereol 1990;70:304-8.
22. Ergun T. Systemic treatment of psoriasis: Rational use of therapeutics and controversial issues. Review. Turk J Dermatol 2007;1:8-14.
23. Adulcikas J, Sonda S, Norouzi S, Sohal SS, Myers S. Targeting the zinc transporter ZIP7 in the treatment of insulin resistance and type 2 diabetes. Nutrients 2019;11:408.