Transepidermal Water Loss (TEWL)-decreasing Effect by Administration of Zinc in the Elderly People

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In recent years, it has become clear that zinc deficiency is closely related in several skin disorders. In elderly people, chronic itch and dry skin are common. In addition, the zinc concentrations are known to decrease with age. Therefore, we examined the beneficial effects of oral zinc supplementation on dry skin and itch in elderly people. Patients 65 years of age or older who visited the Jose Clinic (Odai-town, Mie Pref.) with serum zinc concentrations below 80 μg/dL were enrolled in the study (low zinc group). The participants were administered zinc acetate hydrate for 12 weeks from the start of the study, and transepidermal water loss (TEWL) and stratum corneum moisture content measurements, blood collection, and itch evaluation were performed every 4 weeks. Patients in the control group had serum zinc concentrations of ≥80 μg/dL (the normal zinc group). Results showed that TEWL was significantly higher in the low zinc group than in the normal zinc group, indicating that skin barrier function is impaired in the low zinc group. Serum zinc concentrations increased and TEWL decreased significantly over the 12 weeks of treatment. In addition, a negative correlation was observed between serum zinc concentrations and TEWL. Our results indicate that zinc supplementation is effective to improve the skin barrier function in elderly people.

Key words—zinc; skin barrier function; transepidermal water loss; itch; elderly people; serum zinc concentration

INTRODUCTION

Zinc is an essential trace element for humans.1) It is vital for several biological processes and is crucial for the functions of more than 300 enzymes in the human body.2) Therefore, zinc deficiency is known to cause a variety of symptoms including taste disorder, anorexia, growth retardation, and neuropsychiatric symptoms.3) Substances in foods that have chelating activity, such as phytate,4) as well as several medicines,5) are known to cause zinc deficiency, which is one of the risk factors for skin disorders. For example, acrodermatitis enteropathica is a skin disorder known to be caused by zinc deficiency. Further, recent studies have shown that Langerhans cells (LCs) are significantly reduced in the epidermis and that irritant contact dermatitis is increased in zinc-deficient mice.6) It was also reported that the administration of zinc sulfate is effective to relieve pruritus in hemodialysis patients7,8) and that a reduction in serum zinc concentrations is involved in the onset of pruritus in patients with varicose veins.9) Therefore, it has become clear that several skin disorders are closely related to zinc deficiency.

Dry skin is common in the elderly and they often complain of chronic itch. In clinics, we frequently meet elderly people who are not receiving an appropriate treatment despite complaints that include not only skin effects, such as scratches and infections due to itching dry skin, but also adverse effects to their daily lives such as sleep disorders and decreased concentration. In addition, serum zinc concentrations are known to decrease with aging.10,11) Therefore, we examined the relationship between serum zinc concentration and skin conditions (skin barrier function and dry skin) in elderly people. Furthermore, we examined the beneficial effects of oral zinc supplementation for skin conditions by administering a zinc preparation to patients with low serum zinc levels and evaluating their skin conditions.

METHODS

Participants Patients 65 years of age or older who visited the Jose Clinic (Odai-town, Mie Pref.)
between October 2018 and February 2019 and with serum zinc concentrations below 80 μg/dL (based on the criteria of ‘Practice Guideline for Zinc Deficiency’). 12) were enrolled in this study (the low zinc group). Written informed consent was obtained from each participant. This study was approved by the institutional review board of the Suzuka University of Medical Science (Approval No. 341, July 27, 2018).

The participants were administered zinc acetate hydrate (Nobelzin® tablets) at 100 mg/d for 12 weeks from the start of the study, and TEWL and stratum corneum moisture content measurements, blood collection, and itch evaluations were performed every 4 weeks. At the time of blood collection and skin condition measurements, press through pack (PTP) sheets of Nobelzin® tablets administered to that point were collected and used to assess medication compliance.

Serum zinc concentrations based on blood samples collected from participants were measured. Blood samples, collected using BD Vacutainer® blood collection tubes, were centrifuged at 3000 rpm for 10 min using a KA-1000A (KUBOTA Corporation: Tokyo) centrifuge, and serum samples were obtained. Blood was collected between 9 am and 11 am to reduce the effects of the circadian rhythm on serum zinc concentrations. 13,14) On the day of testing, the patients did not have breakfast and therefore had not eaten the night before. The control group was a group having a serum zinc concentration ≥80 μg/dL or more and were 65 years of age or older (the normal zinc group).

Skin Conditions TEWL and stratum corneum moisture content, which are indicators of skin barrier function and dry skin, respectively, were non-invasively measured. TEWL and stratum corneum moisture content were measured using a Tewameter TM300 and Corneometer CM 825 (Courage + Khazaka Electronic, Köln), respectively, on the inside of the forearm. Mean values of three measurements were used for analysis. The room in which measurements were performed was maintained with controlled temperature (17.1℃ and 25.8℃) and humidity (33.7% and 50.1%), and the participants were asked to stand for approximately 15 min with their forearm exposed to get acclimated to the conditions of the room before measurements were taken.

Itch Assessment Evaluations of itch severity were performed using Shiratori’s criteria. For the low zinc group, evaluation was performed at the same time as skin condition measurements and blood collection every 4 weeks.

Statistical Analysis Comparisons of baseline serum zinc concentrations, TEWL, and stratum corneum moisture content in the normal zinc and low zinc groups were examined using Student’s t-test. Repeated-measures-ANOVA was used to analyze variations in zinc concentration, TEWL, and stratum corneum moisture content before and during Nobelzin® administration to the low zinc group. The correlation between serum zinc concentrations and TEWL was tested by assessing the Spearman’s correlation coefficient. Statistical significance was established at p < 0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, version 1.33), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, version 3.3.1). More precisely, it is a modified version of R commander (version 2.3-0) designed to add statistical functions frequently used in biostatistics. 15)

RESULTS

The study group had 9 patients (3 males, 6 females, age: 78.89 ± 5.75 years). The control group had 9 patients (3 males, 6 females, age: 80.11 ± 3.98 years). Patients background is shown in Supplementary Table 1. Based on the subjects’ medication history and the number of PTP sheets collected after taking Nobelzin® (the collection rate of PTP sheets for all subjects was 80.3% on average), it was judged that the subjects had good compliance. There were no symptoms considered to be side effects of Nobelzin®.

The measured values before and 4, 8, and 12 weeks after taking Nobelzin®, respectively, were as follows: serum zinc concentrations (μg/dL): 76.25 ± 11.59, 111.88 ± 29.78, 130.84 ± 42.61, 116.86 ± 36.33; TEWL (g/m²・h): 12.06 ± 2.63, 10.92 ± 2.53, 8.41 ± 1.69, 9.60 ± 1.97; stratum corneum moisture content (a.u.): 44.44 ± 8.47, 43.70 ± 5.91, 41.30 ± 7.03, 45.30 ± 6.46; Shiratori’s criteria for evaluating the severity of itch in the daytime: 1.00 ± 0.87, 1.11 ± 1.05, 0.78 ± 0.97, 1.00 ± 0.87, Shiratori’s criteria for evaluating the severity of itch at nighttime: 0.78 ± 0.83, 0.89 ± 0.78, 0.89 ± 0.93, 0.78 ± 0.67. For the normal zinc group, the serum zinc concentration, TEWL, stratum corneum moisture content, Shiratori’s criteria for evaluating the severity of itch
Table 1. Comparison of the Group with Low and Normal Serum Zinc at Baseline

|                | Low zinc group | Normal zinc group | p value |
|----------------|----------------|-------------------|---------|
| Sex            | men 3          | men 3             |         |
|                | women 6        | women 6           |         |
| Age            | 78.89 ± 5.75   | 80.11 ± 3.98      | 0.60    |
| Stratum corneum moisture content (a.u.) | 44.44 ± 8.47 | 42.00 ± 7.86 | 0.53 |
| TEWL (g/m²·h)  | 12.06 ± 2.63   | 9.35 ± 2.63       | 0.04    |
| Serum zinc concentration (ng/mL) | 76.25 ± 11.59 | 107.84 ± 20.60 | 0.001 |

Data are expressed as mean ± S.D. p value based upon Student’s t test. p < 0.05 is shown in boldface.

in daytime and nighttime were 107.84 ± 20.60 μg/dL, 9.35 ± 2.63 g/m²·h, 42.00 ± 7.86 a.u., 0.80 ± 0.97 and 0.20 ± 0.67, respectively. In the low zinc group, before taking Nobelzin®, TEWL was significantly higher, and the serum zinc concentration was significantly lower than those in the normal zinc group (Table 1).

The serum zinc concentration increased significantly 12 weeks after Nobelzin® treatment (p = 0.00048), and there was also a significant difference between baselines values and those 8 weeks after treatment (Fig. 1). TEWL decreased significantly between baseline levels and those 12 weeks after Nobelzin® treatment (p = 0.0078), and there was also a significant difference between values at baseline and 8 weeks after treatment (Fig. 2). There were no significant changes in stratum corneum moisture content and scores based on Shiratori’s criteria during the observation period (Figs. 3 and 4). An analysis of 45 samples (9 in the low zinc group with 4 time points and 9 in the normal zinc group) showed a negative correlation between serum zinc concentrations and TEWL (Fig. 5).

**DISCUSSION**

In the present study, a significant decrease in TEWL with increasing serum zinc levels after treatment was observed in elderly people with low serum zinc levels, suggesting an improvement in skin barrier function. To our knowledge, this is the first report indicating that serum zinc levels are associated with skin barrier function in elderly people.

There was no significant change in stratum corneum moisture content with increased serum zinc con-
centrations. However, this parameter is heavily affected by external conditions such as temperature and humidity. Okada et al. reported that forearm stratum corneum moisture content decreases in winter compared to that in summer.\textsuperscript{16} The current study period was from October to February, when temperature and humidity are lower. Therefore, although the environment at the time of measurement was constantly maintained by an air conditioner, it is conceivable that stratum corneum moisture content could have decreased. We hypothesized that the decrease in TEWL contributed to the maintenance of the stratum corneum moisture content (without a reduction), despite the environment.

Whereas an improvement in skin barrier function was observed, the severity of the itch did not significantly improve during the 12-week observation period. In previous studies of hemodialysis patients, it was reported that itching improved when zinc was administered for 2 months.\textsuperscript{7,8} The participants of this study were non-dialytic elderly patients, and differences in participants’ background, compared to those of the previous study, are likely to be the cause of these contradictory results. In addition, it was considered that no significant improvement occurred because the Shiratori’s criteria scores at baseline were not high. However, due to the improvement in the skin barrier function, it was estimated that skin irritability improved and that patients were less likely to develop an itch.

The skin barrier function is known to be regulated by tight junctions, which facilitate the adhesion of adjacent cells \textit{via} proteins, such as claudin\textsuperscript{17} and occludin.\textsuperscript{18,19} The skin is composed of the epithelium, dermis, and subcutaneous tissue in that order.
from the surface inward; the epithelium is further subdivided into the stratum corneum, stratum granulosum, stratum spinosum, and stratum basale in that order from the surface inward. The stratum granulosum is a layer in which flat keratinocytes are stacked, and the resident keratinocytes are identified as SG1, SG2, and SG3. In the skin, tight junctions have been confirmed to be present in the SG2 layer. In addition, claudin-1 is expressed on the surface of LCs in the epithelium; thus, it is thought that there is an association between LCs and tight junctions. LCs are antigen-presenting cells present in the epidermis that function by extending their dendrites across the tight junctions to acquire antigens present outside the barrier.

It has been reported that LCs disappear from the lesions of acrodermatitis enteropathica, which is one of the zinc deficiency-related pathology that can be relieved by zinc administration. These reports suggest the possibility that zinc is associated with skin barrier functions.

Similar to that in the skin, the barrier function of the intestinal epithelium is also regulated by the tight junctions. Many foreign substances such as bacteria, bacterial toxins, and food antigens, among others exist in the intestinal lumen, and this barrier function plays a role in preventing these substances from invading the human body. In the intestinal tract, it has been reported that zinc regulates the expression of occludin via GPR39, a G protein coupled receptor, and enhances intestinal barrier functions. This implies that a similar mechanism might also exist in the skin. Thus, it was considered that zinc could improve the skin barrier function through GPR39 and LCs as serum zinc concentrations increase.

In recent years, the association between zinc and pressure ulcers has gained attention. Moreover, it has long been thought that the pressure sore-healing effect of zinc is due to its involvement in skin metabolism. Higashiguchi et al. reported that the daily administration of dietary supplements containing zinc significantly reduces the incidence of pressure sores. It has also been reported that dry skin is associated with the incidence of pressure sores in lower limbs. This study shows that oral zinc supplementation to elderly people with decreased serum zinc concentrations can improve the skin barrier function, which might contribute to the prevention of pressure sore.

Zinc is contained in many common foods, it is an element familiar to the general consumer, and it has also been widely used as a supplement in recent years. The physiological function of zinc in the skin has long been of interest, and several studies have been conducted, particularly in relation to itch. In contrast, physiological functions with respect to the skin barrier function have hardly been studied to date. Nevertheless, events that suggest its relevance to this process are frequently observed, such as the development of acrodermatitis enteropathica and increase in irritant contact dermatitis. The present study has clarified the beneficial effects of zinc on the skin barrier function and provides new evidence for this role.

CONCLUSION

In our study, oral zinc supplementation to elderly people with decreased serum zinc concentrations did not alter the severity of itch, but decreased TEWL and helped to maintain the stratum corneum moisture content. It is therefore considered that zinc supplementation can improve the skin barrier function.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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