Acta Derm Venereol 2014; 94: 558–562

CLINICAL REPORT

Hair Zinc Levels and the Efficacy of Oral Zinc Supplementation in Children with Atopic Dermatitis

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Zinc deficiency in patients with atopic dermatitis (AD) and the use of zinc supplementation is still controversial. We measured hair zinc levels in 58 children with AD and 43 controls (age range 2–14 years). We also investigated the efficacy of oral zinc supplementation in AD patients with low hair zinc levels by comparing eczema assessment severity index (EASI), transepidermal water loss (TEWL), and visual analogue scales for pruritus and sleep disturbance in patients receiving zinc supplementation (Group A) and others not receiving supplementation (Group B). At baseline, the mean zinc level was significantly reduced in AD patients (113.1 μg/g vs. 130.9 μg/g, $p=0.012$). After 8 weeks of supplement, hair zinc level increased significantly in Group A ($p<0.001$), and EASI scores, TEWL, and visual analogue scales for pruritus improved more in Group A than in Group B ($p=0.044$, 0.015 and <0.001, respectively). Thus, oral zinc supplementation may be effective in AD patients with low hair zinc levels. *Key words: atopic dermatitis; hair; zinc.*

Accepted Sep 18, 2013; Epub ahead of print Jan 28, 2014

Acta Derm Venereol 2014; 94: 558–562.

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Zinc is one of the essential trace elements necessary for the normal cell growth, proliferation, and regeneration in humans. Zinc deficiency can lead to specific skin disorders such as xerosis, acrodermatitis enteropathica (1, 2). Although the relationship between zinc deficiency and atopic dermatitis (AD) is not clear, a zinc deficient diet induced AD-like eruptions and deterioration of skin barrier function in DS-Nh mice (3). In some studies, serum zinc levels were lower in children with AD than in controls (4–6). Moreover, the reductions in serum zinc levels in AD did not correlate with the severity of eczema and might be interpreted as non-specific findings accompanying the skin disorder (5). Therefore, the status and role of zinc in AD is unclear. Furthermore, there has been no study of the efficacy of oral zinc supplementation in zinc-deficient atopic patients.

The mineral content of blood cells has been measured in many studies; however, the procedure is complex and the results are variable (7). On the other hand, hair is easily available, and it is possible to measure essential trace elements with appropriate specificity, sensitivity, speed and procedural simplicity (8). The use of hair for tissue mineral analysis rather accurately reflects the mineral status of the human body (9, 10). This study was undertaken to evaluate the relationship between hair zinc levels and AD and to assess the usefulness of oral zinc supplementation in AD patients with low hair zinc levels.

MATERIALS AND METHODS

Patients

A total of 58 children (28 boys, 30 girls; mean age 6.2 years, range 2–14 years) with confirmed diagnoses of AD according to the criteria of Hanifin & Rajka (11) and with mild to moderate disease (Eczema Area and Severity Index (EASI) score <26), were enrolled in this study. A sex- and age-matched control group consisted of 43 children without dermatological disorders (Table I). Sample size (58 patients with AD and 43 normal controls) was calculated to have power of 80% and detect a difference of 15% in the primary outcome ($\alpha = 0.05$). Exclusion criteria were the use of topical calcineurin inhibitors, or topical steroids or antibiotics in the previous 2 weeks and any systemic anti-inflammatory treatment in the previous 4 weeks. All these medications were prohibited until the end of this study.

The first stage of the study was a comparison of the hair zinc levels of the atopic patients and the control group. The second step consisted of an evaluation of the clinical efficacy of oral zinc supplementation therapy in the atopic patients with low zinc levels and on clinical correlates.

Table I. *Demographic characteristics and hair zinc levels of patients with atopic dermatitis (AD) and controls*

Characteristic	AD ($n=58$)	Controls ($n=43$)	*p*-value
Gender, *n*			0.511
Female	30	23	
Male	28	20	
Age, years, mean ± SD	6.21 ± 2.97	6.74 ± 2.24	0.322
Range	2–14	2–14	
Hair zinc levels, μg/g, mean ± SD	113.10 ± 33.36	130.90 ± 36.63	0.012*
Zinc deficiency, *n* (%)[a]	41 (70.69)	18 (41.86)	0.003*

*$p<0.05$.
[a]Zinc deficiency <130 μg/g. For all individual zinc values see Fig. S1[1].

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1772

This study was undertaken in the outpatient dermatology clinic of Hanyang University Hospital between July 2011 and April 2012. All patients provided written informed consent, and the study protocol was approved by the ethics committee of Hanyang University Hospital.

Measurement of hair zinc levels

Prior to the analysis of hair minerals, all participants were asked not to chemically process their hair for at least 8 weeks. This included dyeing, perming, straightening, or frosting. The hair also had to be free of all gels, oils, and hair creams before sample collection. Approximately 150 mg of the proximal portion of hair was obtained from 4 to 5 different locations on the posterior vertex and occipital regions of the scalp using stainless steel scissors. Hair samples were sent to US TEI (Trace Elements, Inc., Dallas, TX, USA) through Korea TEI. Measurements were performed using a microwave temperature-controlled digestion technique and Perkin-Elmer Mass Spectrometer (Sciex Elan 6100, Perkin-Elmer corporation, Foster, CA, USA) (12). Mineral concentrations are shown as mg% (mg/100 g of hair). By reference to standard levels determined by TEI, hair zinc levels below 130 μg/g were considered to indicate zinc deficiency in this study.

Clinical evaluation of zinc supplementation for atopic patients with low zinc levels

The atopic patients with low zinc levels were randomly assigned to Group A or B. In Group A, supplementation with oral zinc oxide tablets (Zn-TZA plus®, Douglas Laboratories, PA, USA), 12 mg as zinc, was used as a therapeutic regimen for 8 weeks, accompanied by oral antihistamines and topical moisturisers. Patients in Group B received the oral antihistamines and topical moisturisers but no zinc supplementation.

Patients were evaluated by the blinded, independent dermatologist at the start of the study and after 2, 4 and 8 weeks. EASI score, transepidermal water loss (TEWL), and visual analogue scale (VAS) for pruritus and sleep disturbance were assessed at each visit. EASI is a validated score system that incorporates severity of dermatitis and surface area involvement, with a possible total score ranging from 0 to 72 (13, 14). TEWL was measured after subjects were stabilised for 30 min in a climate- and humidity-controlled room. All subjects were instructed not to use moisturiser within 1 h of measurement. TEWL was measured using a Tewameter TM210® (Courage & Khazaka, Germany) over the bilateral antecubital and popliteal fossae. Pruritus severity and sleep disturbance were evaluated at each visit using a VAS (on a 10-point scale with 0 representing absence of pruritus/sleep disturbance and 10 the most severe pruritus/sleep disturbance ever experienced).

Statistical analyses

The chi-square test and Wilcoxon rank sum test were used to compare hair zinc levels. Changes in EASI score, TEWL and VAS over time were analysed by the Wilcoxon rank sum test. Statistical analyses were conducted using IBM SPSS statistics (Ver. 20, NY, USA) and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline hair zinc levels of atopic patients and controls

Mean hair zinc level was 113.10 ± 33.36 μg/g in the atopic patients ($n = 58$) group and 130.90 ± 36.63 μg/g in the control group ($n = 43$) ($p = 0.012$). Forty-one (70.7%) atopic patients had zinc levels under 130 μg/g in contrast to 18 (41.9%) in the control group ($p = 0.003$) (Table I).

Clinical efficacy of zinc supplementation for atopic patients with low zinc levels

Of the 41 atopic patients with low hair zinc levels, 22 were randomly allocated to Group A (oral zinc supplementation group) and 19 to Group B. Baseline demographic data and EASI scores did not differ significantly between groups A and B (Table II).

Hair zinc level after oral supplementation

In Group A, hair zinc level increased from a baseline value of 96.36 ± 21.05 μg/g to 131.81 ± 27.45 μg/g after 8 weeks of oral zinc supplementation ($p < 0.001$). In Group B, the level did not change significantly (Fig. 1a).

EASI score

In Group A, baseline EASI score was 6.56 ± 3.12 and it improved to 4.23 ± 2.04 at 2 weeks, 2.68 ± 1.46 at 4 weeks and 1.73 ± 1.23 at 8 weeks. In Group B, baseline score was 6.32 ± 2.80 and it declined to 5.24 ± 2.94 at 2 weeks, 4.56 ± 2.67 at 4 weeks, and 3.29 ± 2.77 at 8 weeks. The EASI scores at 4 weeks and 8 weeks differed significantly between Group A and B ($p = 0.013$, 0.044, respectively) (Fig 1b).

TEWL

We measured TEWL, to evaluate skin barrier function. In Group A, the baseline value of TEWL was 23.62 ± 8.13 g/m^2/h and it declined to 21.33 ± 6.99 at 2 weeks, 18.71 ± 6.67 at 4 weeks, and 15.19 ± 5.67 g/m^2/h at 8 weeks. In Group B, baseline TEWL was 23.78 ± 7.21 and it was 22.38 ± 5.81 at 2 weeks, 20.94 ± 4.66 at 4 weeks and 19.86 ± 4.68 at 8 weeks. At 8 weeks, TEWL differed significantly between Group A and B ($p = 0.015$) (Fig 1c).

VAS for pruritus and sleep disturbance

Pruritus score before treatment was 3.95 ± 1.89 in Group A and 4.47 ± 1.74 in Group B. In Group A, it declined to 2.73 ± 1.45 at 2 weeks, 1.90 ± 0.81 at 4 weeks, and 1.09 ± 0.29 at 8 weeks. In Group B, the visual analogue scale (VAS) score for pruritus also decreased in Group

Table II. *Baseline characteristics of AD patients with low levels of hair zinc (< 130 μg/g) who were subsequently supplemented with oral zinc (Group A) or not (Group B)*

Characteristic	Group A ($n = 22$)	Group B ($n = 19$)	*p*-value
Gender, *n*			0.278
Female	9	11	
Male	13	8	
Age, years, mean ± SD	5.36 ± 3.03	5.89 ± 2.03	0.521
Range	2–11	3–9	
EASI score (baseline), mean ± SD	6.56 ± 3.12	6.32 ± 2.80	0.800

EASI: eczema area and severity index; SD: standard deviation.

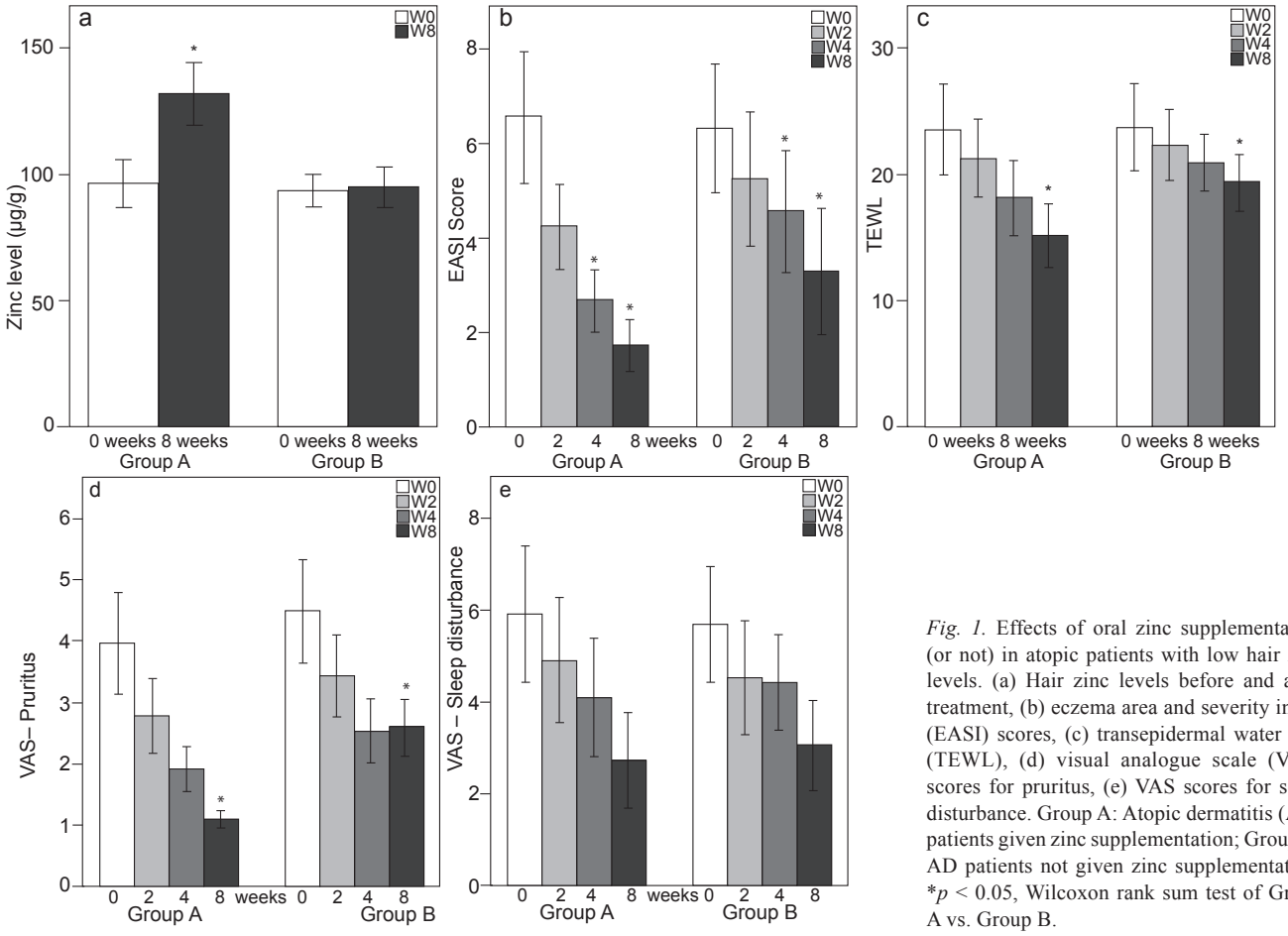

Fig. 1. Effects of oral zinc supplementation (or not) in atopic patients with low hair zinc levels. (a) Hair zinc levels before and after treatment, (b) eczema area and severity index (EASI) scores, (c) transepidermal water loss (TEWL), (d) visual analogue scale (VAS) scores for pruritus, (e) VAS scores for sleep disturbance. Group A: Atopic dermatitis (AD) patients given zinc supplementation; Group B: AD patients not given zinc supplementation. *$p < 0.05$, Wilcoxon rank sum test of Group A vs. Group B.

B but not as much as in Group A. The VAS scores at 8 weeks differed significantly ($p < 0.001$) (Fig. 1d). Baseline VAS score for sleep disturbance was 2.86 ± 1.87 in Group A and 2.84 ± 1.30 in Group B. In Group A, it declined to 2.36 ± 1.65 at 2 weeks, 1.86 ± 1.64 at 4 weeks, and 1.36 ± 1.18 at 8 weeks. In Group B, the corresponding scores were 2.26 ± 1.28, 2.21 ± 1.08, and 1.53 ± 1.02, and there were no significant differences between the 2 groups (Fig. 1e).

Side effects

No complications occurred in any of the patients during the follow-up period.

DISCUSSION

Zinc is an important micronutrient; it is an essential component of many metalloenzymes involved in a variety of metabolic pathways and cellular functions (15, 16). Because of its immunomodulatory effects, zinc is increasingly studied in inflammatory diseases such as AD (17).

Although total body zinc is stored primarily in the bones, muscles, prostate and skin, there is no free exchange of stored zinc, and metabolic needs must be met by a continual supply of dietary zinc (1, 18–21). In persons with zinc deficiency, specific eruptions such as xerosis cutis, acrodermatitis enteropathica and hair loss occur, and wound healing is poor (1). A previous study has suggested that zinc deficiency may induce AD-like conditions (3). Mice fed a zinc-deficient diet had wider and more severe skin lesions than controls, and TEWL was markedly increased (10.8 vs. 5.5 g/m^2). Higher immunoglobulin E (IgE) levels, and increased interferon γ (IFNγ) and interleukin-13 (IL-13) production were also seen. In a human study, a mild deficiency of zinc led to reduced Th1 functions, as measured by the production of IFN-γ, IL-2, and tumour necrosis factor-α (TNF-α), whereas Th2 functions were not affected. Thus, zinc deficiency in humans results in an imbalance between Th1 and Th2 cells (22, 23). In a cell culture model, zinc deficiency decreased NF-κB activation, leading to reduced generation of inflammatory cytokines including TNF-α, IL-1β and IL-8. These data suggest that zinc deficiency may reduce anti-inflammatory effects and cause a relative increase of Th2 cytokines, which are the cytokines mainly implicated in AD (24).

Until now, a few contradictory results have been reported about the levels of zinc in atopic patients compared to control (4–6). Di Toro et al. (25) found no differences in serum levels, although zinc levels in hair were lower in patients with AD. An Asian study showed decreased

serum zinc level in AD patients and they suggested that the empirical avoidance of seafood and meat in Hong Kong may be the possible cause (26). In Korean normal population, mean zinc intake has increased during the 1990s with a marked decrease of cereal consumption and an increase of meat and fish (27). The daily mean intake of zinc was more than that of the Korean Dietary Reference Intake (KDRI) and zinc absorption and balance were favourable in children (28, 29). Therefore, it is postulated that increased demand or redistribution of zinc in response to inflammation may be the possible aetiology for the zinc deficiency in AD patients.

Because there have been no consistent data on zinc levels in atopic patients and no established methods of measuring zinc in humans, the first aim of this study was to measure zinc levels in atopic patients and controls by analysing hair. The serum concentration of zinc has been the most commonly used indicator of zinc status (7). However, it is influenced by a variety of factors, such as infection, stress, pregnancy, and growth rate, which limit its diagnostic value (2, 30, 31). Moreover, blood levels of minerals do not directly reflect tissue levels. Mineral levels in the blood are more strictly regulated than in other tissues, and excess mineral in the blood is rapidly excreted, so that the value of measuring serum concentrations of zinc is low (7, 31).

On the other hand, the level of a mineral accumulated in solid, non-regenerating tissues such as hair is a more stable and longer-term indicator of general tissue levels (10, 32, 33). Human hair is a convenient source, being easy to obtain and robust, and its storage and preparation for analysis are straightforward since no special preservation techniques are required. The nutrient source for hair growth is the blood supply, which contains traces of anything ingested by the individual (9, 34). Moreover, the concentrations of trace elements in hair are at least 10 times higher than in blood, serum and urine (10). Hair analysis is commonly used in the study of nutrition, dietary habits, exposure to toxins, and drug abuse (10, 35). The concentration of zinc in hair is generally regarded as a good indicator of zinc status in children. Almost all previous studies of atopic patients measured serum zinc levels (4, 26). Although there is only one study that evaluated zinc levels in hair, the aim of that study was to assess the effect of parental history of AD and hair mineral level on the risk of newborn infants developing AD during the first month of life (35).

There are no current guidelines regarding zinc supplementation on which to base clinical recommendations. One previous study evaluated the efficacy of oral zinc supplementation in atopic patients and found no clinical improvement in disease severity or subjective symptoms (36). In that study, however, the authors did not check the patients' baseline zinc levels and reached a negative conclusion regarding the effect of oral zinc supplementation in atopic patients. On the other hand, in our study, we first compared baseline zinc levels in atopic patients and controls, and then examined the effect of oral supplementation on a group of the atopic patients with low zinc levels. We found that the proportion of individuals with low zinc levels was higher among the atopic patients than the controls, and the mean hair zinc level was also lower in the atopic patients. After oral supplementation for 8 weeks, the mean hair zinc level in the zinc supplemented group had reverted to the normal range, whereas that of the unsupplemented group remained low.

To obtain objective data, we evaluated clinical efficacy by measuring EASI scores and TEWL. Generally, all the parameters we measured improved gradually in both groups. However, at 8 week follow-up, EASI scores, TEWL, and VAS for pruritus had statistically significantly improved more in the oral supplementation group than in the group without supplementation. Changes observed in non-supplemented group could be explained by the concomitant use of oral antihistamines and topical moisturisers along with thorough education. Because the clinical parameters improved continuously after treatment over the study period without evidence of any plateau, we might anticipate greater improvement if the period of study was longer.

Collectively, we proved that there is a correlation between AD and hair zinc level and AD patients with low hair zinc level showed clinical improvement after oral zinc supplementation. Although it is not easy to compare directly the values obtained from serum and hair, and there are many factors that influence the results, we obtained consistent and significant results indicating that zinc plays a critical role in AD and should be taken into account when physicians treat atopic patients.

However, there should be a consideration of side effect of zinc supplementation when determining the therapeutic range of zinc. Clinical features associated with acute zinc toxicity include gastrointestinal symptoms and dizziness, while those associated with chronic toxicity include haematological abnormalities such as anaemia and neutropaenia (37). If excessive zinc hinders intestinal copper absorption, copper deficiency can occasionally be induced. A case of chronic zinc toxicity has been reported in an infant who presented with anaemia and neutropaenia after zinc therapy. However, in that case, 45 mg/day of zinc was administered to treat the AD and this dosage is 9 times the daily dietary allowance for zinc for this age group (38).

We suggest that a zinc supplement of 10–20 mg/day may be effective in treating zinc deficient atopic patients until normal levels are restored (37–39). After that, the daily recommended dosage according to age (1–8 years: 3–5 mg/day, 9–14 years: 8 mg/day, >15 years: 9–10 mg/day) may be appropriate as maintenance treatment.

The main limitations of this study were the relatively small number of patients and the short follow-up time. Future studies that assess the effects of oral zinc supplementation according to treatment dose and duration, and provide long-term maintenance treatment, will test

the proposed therapeutic role of oral zinc supplementation in AD.

ACKNOWLEDGEMENT

The authors thank Korea TEI, Inc. for help with measuring hair mineral levels.

The authors declare no conflict of interest.

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