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Review Article

Zinc as an essential element for normal immune reactions and as a therapeutic agent for autoimmune diseases

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Abstract Zinc is an essential element that is involved in more than 300 enzymes metabolism. Also, zinc is engaged in the function of many immunological processes as zinc deficiency leads to a reduction in T-cells, altered T-cell differentiation, and suppression of their functions. Zinc deficiency causes impairment of the immune system, increased susceptibility to infections and an escalation to chronic inflammation if untreated. In addition, there are many studies that had been carried out and showed that zinc is an important therapeutic agent in the treatment of many cuteness and systemic disease either in a form of topical zinc cream or through oral zinc sulfates like in therapy of alopecia areata, vitiligo, psoriasis and systemic sclerosis. So the aim of this review is to illustrate and highlight the role of zinc in health and disease.

Key words
Zinc, zinc sulfate, immune reactions, autoimmune diseases.

Introduction

Since the severe consequences of zinc deficiency were first described by Prasad *et al*. in the 1960s, the importance of zinc in biological processes has been identified.[1] Zinc is an essential component of more than 300 enzymes[2] and over 2000 transcription factors.[3] It is involved in processes such as cell signalling, redox regulation, cell proliferation, differentiation, survival and immune response.[4] In the immune system, zinc effects the generation of T-lymphocytes at different stages, as shown in **Figure 1**.[5]

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Thus, zinc deficiency leads to a reduction in T-cells, altered T-cell differentiation and suppression of their functions. In autoimmunity, the balance between two particular subsets of T-cells-regulatory T-cells (Treg) and T helper type 17 cells (Th17) is disrupted so that Th17 cells are up regulated. Treg cells are responsible for down regulating inflammation to maintain immune homeostasis. Conversely, Th17 cells promote inflammation by inducing many pro-inflammatory cytokines and activating many cell types, notably those usually involved in fighting infections.[6]

In short, zinc deficiency causes impairment of the immune system, increased susceptibility to infections and an escalation to chronic inflammation if untreated.[7] Unlike iron, there is no storage system for zinc in the body. Hence, a continuous external supply is necessary to carry out the crucial functions in the body.[8-9]

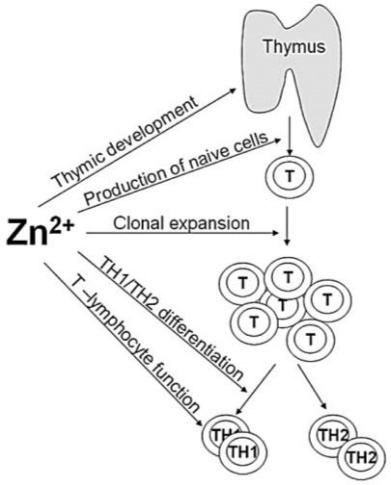

Figure 1 Zinc influences the different levels of t-lymphocyte generation. (adapted from reference 5). zinc affects the development of thymus, production of naïve cells, clonal expansion of t-cells, differentiation of t-cells into th1 or th2 cells and function of the t-lymphocytes.

Zinc supplementation has been used to treat bacterial, viral and parasitic infections and autoimmune diseases in various small-scale clinical studies.[10-20] In this review, the effectiveness of oral or topical $ZnSO_4$ treatment for skin conditions caused by autoimmune reactions are discussed.

Use of zinc sulfate in diseases with auto-immune reactions

Various forms of zinc, whether elemental or as salts, have been used as therapeutic agents for centuries.[9]

Vitiligo

Vitiligo is a common depigmenting skin and hair disorder with an incident rate of 0.1-2% regardless of age, race, ethnicity or skin colour.[21-25]

Yaghoobi *et al*. conducted a randomised clinical trial to evaluate the efficacy of combinatory therapy using oral zinc sulfate and topical corticosteroid.[18] Topical corticosteroid cream was given to two groups, the first containing 16 people and the second with 19 people. The second group also received two capsules of zinc sulfate (each containing 220 mg) twice daily for teenagers and adults or a dose of 10 mg/kg as a capsule or syrup for children. In the second group, the serum zinc level was monitored at 1 and 3 months after the treatment. The largest patch of depigmentation was used as the target lesion for all participants and its size was measured after 1, 3 and 4 months.

In both groups, there was no response to treatment observed in the first month. The final mean responses from the first and second groups were 21.43% (±11.6%) and 24.7% (±11.0%), respectively, which were not statistically significant. Therefore, zinc sulfate had no benefit when use in conjunction with topical corticosteroid treatment. Moreover, the serum zinc level in most participants was within the normal range, which was in agreement with the findings by Arora *et al*.[26]

Psoriasis

Psoriasis is a chronic inflammatory autoimmune-mediated disorder of the skin affecting nearly 2% of the general population with a high relapsing rate.[27-28] A further complication manifests in the inflammation of joints. Currently, available treatments include topical corticosteroids and tars, phototherapy, systemic treatment of methotrexate and retinoids and biologics such as adalimumab and infliximab.[19]

Sadeghian *et al*. conducted a randomised, double-blind clinical trial of 60 participants to find the effectiveness of topical zinc pyrithione.[19] Group A (30 people) received topical and emollient-based 0.25% zinc pyrithione cream to be applied twice daily. Group B (control, 30 people) received an

emollient cream without zinc. The treatment outcome was measured by using PASI (a measurement tool for psoriasis), determining the severity of induration, erythema and scaling. The percentage reduction of mean PASI scores in groups A and B were 70.5% and 9.3%, respectively. Also, five people from group A were lesion-free at the end of the study (cf. no participants from group B were lesion-free). No side effects were observed from the treatment. Also, Sharquie *et al*. conducted a placebo-controlled study using topical 5% and 10% zinc sulfate cream for topical therapy of psoriasis vulgaris and the results were statistically significantly effective when compared with emollient cream.[29]

Lichen planus

Lichen planus is a chronic inflammatory disease involving the skin, mucous membrane, scalp and nails; it affects 0.5-2.6% of the general population.[30] Factors such as stress, systemic medications, genetics, immunity and hypersensitivity reactions, and viral infections contribute to the manifestation of lichen planus.[31]

Mehdipour *et al*. conducted a randomised, double-blind study to compare the efficacy of mouthwash with or without 0.2% zinc combined with fluocinolone in 20 patients with erosive lichen planus.[20] The duration of the trial was two months. Group A (10 patients) received a placebo mouthwash without zinc, and group B (10 patients) received the mouthwash with zinc three times a day. All participants used fluocinolone ointment twice a day. The treatment outcome was measured by (i) determination of the lesion size by using digital callipers and (ii) pain severity by using a visual analogue scale (VAS).[32]

Pain severity, irritation and lesion surface area decreased in both groups. In particular, the decrease in pain and irritation in both groups was identical, which could be attributed to the effect of fluocinolone use. In contrast, a reduction in surface area in group B (using zinc mouthwash and fluocinolone ointment) was attributed to the effect of zinc.

Recurrent aphthous stomatitis (RAS)

Aphthous stomatitis is a painful oral ulcer characterised as a recurrent inflammatory process of the oral mucosa.[33] Sharquie *et al*. conducted a double-blind, placebo-controlled study to compare the therapeutic and prophylactic effects of oral $ZnSO_4$ compared with dapsone for 12 weeks.[15] Of the 45 patients recruited, 15 patients were allocated for each group (A: $ZnSO_4$ treated; B: dapsone treated; and C: control). Group A was given 150 mg of $ZnSO_4$ twice daily and the Oral Clinical Manifestation Index (OCMI) and measurement of ulcer diameter were used for monitoring the therapeutic outcome of $ZnSO_4$. In short, $ZnSO_4$ demonstrated superior and significant therapeutic and prophylactic effects for reducing the size of RAS in comparison to dapsone.

Alopecia areata (AA)

AA is a disorder that affects hair follicles and sometimes the nails.[16] Complete or nearly complete hair loss can occur in one or more circular or oval nonscarring patches in the hair-bearing area. Numerous medications have been used for treating AA, such as topical, intralesional and systemic corticosteroids; however, they are limited by poor efficacy and toxicity.[34-36] Sharquie *et al*.[16] conducted a randomised, placebo-controlled, double-blind crossover trial using oral $ZnSO_4$ at a dose of 5 mg/kg/day (this daily dose was divided into three amounts). For the treated group (group A, 37 patients), $ZnSO_4$ was given for the first 3

months followed by a 3-month placebo treatment (vice versa for the placebo group (group B, 30 patients)). For group A, 22 patients (59.45%) had "complete hair regrowth". After switching to the placebo, hair growth was maintained in the patients who achieved "complete hair regrowth" in the first 3 months. On the contrary, only three patients (10%) achieved "complete hair regrowth" at the end of the third month for group B. After switching to $ZnSO_4$ treatment, there was a significant increase in the number of patients who had complete hair regrowth.

Behcet's disease (BD)

BD is a chronic relapsing disease characterised by orogenital ulcerations. In addition, the eyes, brain and joints are affected. Autoimmune reactions with vasculitis are well demonstrated in this disease.[17] Sharquie *et al*.[17] conducted a randomised, controlled, double-blind crossover trial of 30 patients to explore the effectiveness of treating BD with 100 mg of oral $ZnSO_4$ three times daily for 3 months followed by placebo treatment for a further 3 months (group A). The placebo-treated group was given a placebo for the first 3 months, then the same dose of $ZnSO_4$ was given for the following months (group B). At baseline, the serum zinc level was significantly lower in BD patients than in healthy individuals.

There was an inverse correlation between the clinical manifestation index (CMI) score and serum zinc level, that is, a decrease in CMI score with increasing serum zinc level in both groups. The erythrocyte sedimentation rate (ESR) also decreased after treatment with $ZnSO_4$ but increased when the patients were switched to the placebo.

Morphea

Morphea, also called localised scleroderma, is a skin disease characterised by thickening of the dermis, subcutaneous tissue or even the underlying muscle due to excessive collagen deposition.[37-38] About half of the patients experience recurrence within 2-7 years from the onset of the disease.[39]

Brocard *et al*. conducted a study to investigate the efficacy of high-dose zinc gluconate for treating morphea.[38] All 17 patients, who had not previously responded well to dermocorticosteroids, received 60-90 mg of zinc metal daily (equivalent to 4-6 Rubozinc capsules) for 12 months. The response rate was 53%, including five partial and four complete remissions. Only two patients had gastric irritation, but there was no discontinuation due to the adverse effect of zinc gluconate.

Sharquie *et al*. investigated the efficacy of intralesional administration of hyaluronic acid in the treatment of patients with sclerosis and used a combination therapy of oral and topical corticosteroids plus oral zinc sulfate to stop the activity of morphea and to maintain remission.[37]

Systemic lupus erythematosus (SLE)

Chronic ulcers on the leg are commonly observed with various autoimmune diseases. In SLE, ulcers are usually acute, and healing occurs as the condition subsides.[40] Wang *et al*. tested the efficacy of oral $ZnSO_4$ for two female patients who had not responded well to conventional treatments such as prednisolone. Both patients were given 750 mg of $ZnSO_4$ daily in divided doses, and their ulcers were successfully healed within 2 months.[40]

Systemic sclerosis

The characteristics of systemic sclerosis are fibrosis and the thickening of various tissues in the skin and internal organs.[41] Zinc levels of

patients with scleroderma are low, especially in erythrocytes, platelets and granulocytes.[42] Penicillamine treatment increases intestinal absorption and urinary excretion, and the serum level of zinc increases; however, zinc deficiency might also be promoted due to the complex interaction between zinc and penicillamine.[43] The toxicity of penicillamine is elevated, possibly due to the depletion of copper caused by zinc and penicillamine. Thus, long-term zinc supplementation (15-60 mg/day) should be combined with a copper supplement (1-4 mg/day). In addition, oral zinc sulfate has been used to treat systemic sclerosis through an uncontrolled, prolonged study aiming to stop the progression of the disease, thus inducing remission.[37, 44-45]

Conclusion

Oral application of $ZnSO_4$ provides a versatile, cost-effective treatment, with minor side effects, for a range of dermatological conditions. In all the studies, the serum zinc level was initially low in the patients at the baseline, but it increased quickly with $ZnSO_4$ treatment. Interestingly, in crossover studies, as soon as the subjects were switched to the placebo, the serum zinc level decreased; however, it was maintained higher than the baseline, indicating the prolonged effect of zinc treatment. The molecular mechanisms of zinc in the immune system are not fully understood to date. However, it is speculated that zinc acts as an antioxidant to remove reactive oxygen species (ROS) produced in inflammation,[46] exerts immunomodulatory effects on T-cells,[47-48] is involved in wound healing or directly works on infectious agents.[49] It is still necessary to conduct longer and larger-scale trials to comprehensively determine the effectiveness of oral $ZnSO_4$ application to establish treatment guidelines or recommendations for zinc therapy.[9]

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