ZINC IN DERMATOLOGY
(A Review)

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Summary

Introduction of oral zinc as a therapeutic remedy in several skin disorders is a relatively recent event. A comprehensive account on the important aspects of zinc metabolism in human beings is briefly reviewed. The etiology, clinical features and diagnosis of primary and condition zinc deficiency in man have been described. Finally, the therapeutic role of oral zinc in various skin disorders is discussed.

KEY WORDS: 1. Zinc metabolism. 2. Zinc deficiency. 3. Acrodermatitis enteropathica. 4. Therapeutic role.

From the time of ancient Egyptians, the zinc oxide and other derivatives of zinc have been used to promote wound healing[1]. Zinc forms a major component in several topical formulations. Acrodermatitis enteropathica (AEP) is now considered as a zinc deficiency syndrome and the administration of oral zinc was found to result in complete resolution of the lesions[2-4]. Several recent studies revealed the usefulness of oral zinc in acne vulgaris[5-8]. It was also found effective in the treatment of chronic venous leg ulcers[9], rheumatoid arthritis[10] and psoriatic arthropathy[11]. The initial success observed with oral zinc prompted enthusiasm among clinicians to try the effect of zinc in several skin and systemic disorders. New indications are being added day by day. The purpose of this communication is to provide a comprehensive review on the important aspects of zinc metabolism, deficiency features and therapeutic role in skin disorders, with an idea to rationalize its use in dermatology.

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Historical

Raulin was the first to show in 1869, that zinc is essential for the growth of *Aspergillus niger*[12]. Somer[13] in 1928 demonstrated that it is also essential for higher forms of plant life. Later, Tucker and Salmon[14] established that zinc is necessary for the growth and betterment of different animal species. In human beings, zinc deficiency was first suspected in Iranian males by Prasad et al[15] in 1961. Subsequently, it was confirmed after detailed studies carried out in 1963 by a group of workers in Egypt[16].

Daily Requirements

Zinc is a metal with atomic number of 30 and atomic weight of 65.38. The

minimum requirement of zinc was found to vary with age, functional activity, ambient temperature, diet, parasitic infestation and trauma[17]. The daily requirement of zinc in human beings has been estimated as follows [18,19].

Infants upto 1 year	... 3-5 mg
Children from 1-10 years	... 10 mg
Children above 10 years & Adults	... 15 mg
Pregnancy	... 20 mg
Lactation	... 25 mg

Dietary Sources and Composition

Foodstuffs of animal origin including dairy products and sea foods, legumes, nuts, whole grain, lettuce, soyabean and green leafy vegetables are rich in zinc. Water added for cooking and the type of utensils used to prepare and store food have been found to modify the zinc content of food[20]. It has been stated that during milling process of wheat for flour, zinc content may be lost upto 80%[21]. The amount of zinc present in grains and vegetables has been found to depend upon the soil in which these were cultivated. Price et al[22] showed that zinc concentration in majority of grains and legumes was increased when 20% superphosphate was used as the fertilizer. Due to high phytate and fibre content, the zinc derived from plant origin is less available for utilization and absorption than the zinc derived from animal products. A positive correlation has been noted between the zinc and protein content of the various foods[23].

Distribution in Human Body

The total body content of zinc in man has been estimated to vary from 1.4 to 2.4 gms. The major portion of this is present in muscle tissue which has about 63% of total zinc content. The epidermis contains six times more zinc than the dermis. The skin and its appendages contain about 20% of the total body zinc content. The mean zinc concentration of normal human epidermis and dermis has been reported to be 70.μg and 12.6μg per gram dry weight respectively[24]. Liver, kidney, bone, retina, prostate and muscle appear to be rich in zinc. The zinc concentration of human serum is constantly higher than that of plasma by 16% on an average[25]. Vallee and Gibson[26] reported that 75 to 88% of total human blood zinc is present in RBC, 12 to 22% in the plasma and 3% in WBC. The zinc content of scalp hair in school children was estimated to vary from 125 to 225μg/gram[27]. Vallee and Gibson[26] reported the following normal zinc values using a dithizone method in human beings: 8.8 μg/ml for whole blood, 1.21 μg/ml for plasma and 14.4 μg/ml for erythrocytes. These values were later confirmed by Prasad et al[28] by an atomic absorption method. The major part of plasma zinc (60–70%) is loosely bound to albumin, about 30–40% is firmly bound to α2-macroglobulin and a small portion circulates as ultrafiltrable aminoacid-zinc complexes[29]. The plasma zinc levels in females are a little lower than in males. Slightly lower values of plasma zinc were observed in old age[30] and during pregnancy[31]. The zinc levels in the new born which are similar to those of adults show a slight fall during the first week of life and at second and third month but return towards normal during the fourth month continuing to be the same throughout the remainder period of infancy except for a drop at about first year of life[32].

Physiological Role

Zinc affects the cell membranes of mast cells, platelets and red cells. It prevents the induced histamine release from mast cells. Zinc supplementation was found to inhibit the migration and other activities of macrophages and eventually of polymorphonuclear leucocytes resulting in the stabilization

of membranes[33]. Zinc improves the filtrability of the sickle cells and in fact, the antisickling effect of zinc has been demonstrated in both vivo and vitro by Lux et al[34]. A deficiency of zinc can adversely affect all the phases of cell cycle due to its vital role on DNA synthesis and RNA catabolism[35]. Zinc depletion may result in gonadal dysfunction, probably due to some alteration in the testicular steroidogenesis[36]. Zinc is known to compete with copper, lead, cadmium, iron and calcium for similar binding sites.

Absorption

Major portion of oral zinc is absorbed from the whole of small intestine and is influenced by various factors such as body size, zinc content in the diet and the presence of other interfering substances such as calcium, phytate and vitamin D in the diet. However, the exact mechanism of zinc absorption and transport of zinc in man is not known. Evans et al[37] proposed a zinc binding low molecular weight ligand secreted into the intestine by pancreas that transports zinc into the absorptive mucosal cells. Later, the zinc is removed into portal blood by binding with transferrin and albumin. Uptake of zinc might be partly regulated by the number of binding sites on transferrin and albumin, which probably reflect the zinc need of various tissues[38]. By increasing the daily zinc intake of rats about 16 times, the absorption could increase three times only[39]. The block is probably mediated by the synthesis of a metallothionein in the intestinal wall[40].

Excretion

From the portal blood zinc enters the liver and may be stored temporarily depending upon the zinc status in the body. The turnover rate of zinc is rapid in the pancreas, liver, spleen and kidney. The zinc in these tissues and the more slowly exchanging muscle and red cell zinc form a soft tissue zinc pool. The main excretion of zinc takes place through the gastrointestinal tract. Most of this faecal zinc represents the unabsorbed zinc and additional 5 to 6 mg of endogenous zinc[4]. In tropical areas large amounts of zinc may be lost in sweat. Prasad et al[41] estimated that a normal individual in a tropical area secreting about 4 liters of sweat per day may lose about 4 mg of zinc per day. Urinary zinc constitutes about 10% of daily loss of zinc and has been estimated to be about 0.3 to 0.6 mg/day[42]. Minute quantities of zinc may be lost in saliva, desquamating skin, hair, ejaculate and menstrual bleeding.

Diagnosis of Zinc Deficiency

Laboratory criteria for the diagnosis of zinc deficiency are not completely evaluated. The response to therapy with zinc is probably the most reliable index for establishing a diagnosis of zinc deficiency in man. It is not certain at present whether a low level of plasma zinc is indicative of zinc deficiency. Decreased levels of zinc may reflect an impaired zinc nutrition in many, while in others it may indicate a shift of zinc from plasma to another body pool[12]. The concentration of zinc in hair may reflect the status of chronic zinc deficiency. Urinary zinc levels were found to decrease as the zinc deficiency state progresses. Metabolic balance study, turnover rate and 24 hour exchangeable pool for zinc as measured by Zn_{65} may provide additional tools for indicating zinc status in man[12]. A good correlation between the activity of ribonuclease, carbonic anhydrase and serum alkaline phosphatase and zinc status in the body has been reported[43]. Certain metalloenzymes in blood may be utilized for assessment of zinc status in man. Serum copper levels in many zinc deficiency disorders tend to fluctuate inversely with serum zinc levels and it has been suggested that zinc copper ratio may be used as an index of zinc nutrition in man[4].

Zinc Deficiency

The deficiency of zinc has been noted to result in the impairment of growth and development, decreased resistance to local infection, delayed wound healing, hyperkeratotic skin changes, gastrointestinal disturbances, apathy, depression, behavioural changes and impairment of taste sensation[4]. Two primary zinc deficiency disorders where no other conditioning disease could be recognized, have been described in man. These are endemic nutritional zinc deficiency and acrodermatitis enteropathica.

Endemic nutritional zinc deficiency

Prasad et al[15] suspected the deficiency of zinc as the cause of retarded growth and sexual development in adolescent Iranian males and the condition responded to zinc treatment. Similar observations were reported later from Egypt and Turkey[44,45]. The zinc deficiency was attributed to the diet consisting mainly of vegetables and whole grain bread having a high content of phytate and fibre which interfere with the absorption of zinc. Hookworm infestation and geophagia were blamed as additional factors.

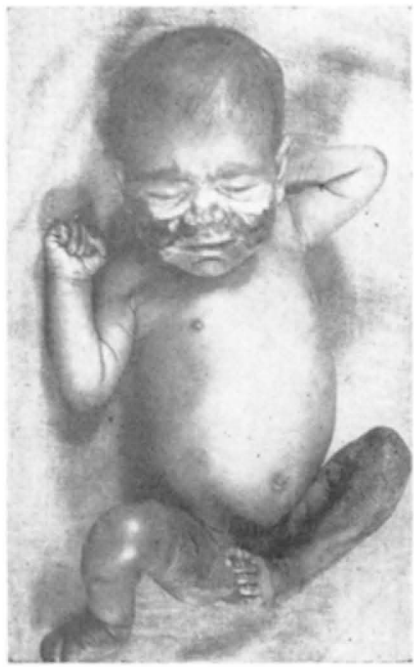
Acrodermatitis enteropathica

This is a zinc deficiency syndrome that starts in early childhood soon after weaning. Clinically the lesions are characterized by dermatitis on acral and periorificial areas of the body and usually associated with diarrhoea and alopecia (Fig. 1). Defective absorption of the zinc in the GI tract has been considered to be responsible for this condition[46]. Evans and Johnson[47] stated that there is a deficiency of zinc binding ligand in the intestinal lumen. The condition responds promptly to the administration of oral zinc.

Conditioned zinc deficiency

The formation of insoluble complexes with calcium, fibre, and phytate

A



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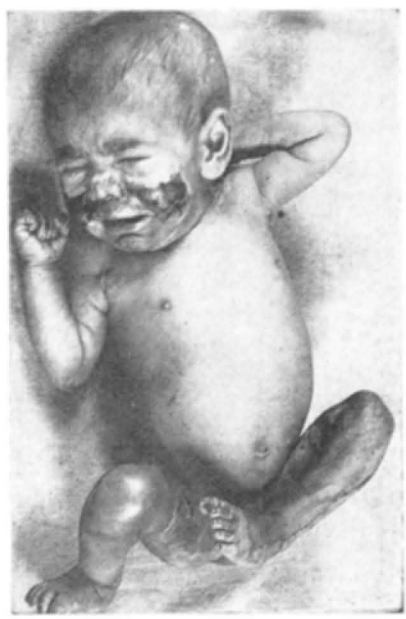

Fig. 1 Acrodermatitis Enteropathica. Note the alopecia on scalp and dermatitis on acral portions. The child had diarrhoea also.

markedly decrease the intestinal absorption of zinc[48]. Alcohol consumption has been mentioned to result in increased excretion of urinary zinc[49]. A decrease in the plasma zinc levels was observed in women on oral contraceptives and pregnancy. Low zinc levels were reported in cirrhosis of liver and viral hepatitis[50], neoplastic conditions, parasitic infestations, acute infections and following myocardial infarction[12,51]. A zinc deficient state was also reported in steatorrhoea[52], renal failure[53], severe burns[54] and mongolism[55]. In pregnant rats zinc deficiency may lead to foetal abnormalities, behavioural impairement of the offspring and difficulty in parturition of the mother[56]. A state of zinc deficiency was noted after the administration of penicillamine and total parenteral nutrition[17] and similarly with antimetabolites and antianabolics[57].

Cutaneous lesions in zinc deficiency

These features were extensively described by Weismann[4] under two categories (acute and chronic).

Acute zinc deficiency

The early skin lesions appear as inflammatory papules that may coalesce to form erosive, well-defined plaques with satellite lesions around the anogenital region. The lesions around the eyes, nose and mouth may result in crusting and appear as black necrotic areas. The condition may resemble seborrheic dermatitis in adults. Severe zinc deficiency may manifest in the form of flaccid bullae on the flexural creases of fingers and hands which may leave a typical peripheral collarette of scales after rupture. There may be paronychial changes. Severe inflammation and desquammation may develop on the feet.

Chronic zinc deficiency

This is characterized by well-defined brownish red, thickened, eczematous and moderately scaly lesions. They may appear as either verrucous or psoriasiform lesions and are usually seen over the bony prominences, flexural and mucocutaneous areas. Following severe bouts of zinc deficiency, there may be total loss of hair and nails. The hair loss starts in the occipital region and may involve rest of the scalp. The hair may be loose, fragile and depigmented. The nails may show chronic paronychia and other patterns of nail dystrophy. The nail plates may be uneven and show multiple transverse depressions resembling Beau's lines.

Oral Zinc in Skin Disorders

Acrodermatitis Enteropathica:- Now, it is well established that this condition is a zinc deficiency disorder and usually starts in early childhood. Moynahan[46] assumed that zinc deficiency results from the defective absorption of zinc in the intestines, probably due to the formation of unabsorbable zinc-peptide complexes in the intestinal lumen. Several studies revealed that administration of oral zinc results in rapid improvement of skin lesions and general condition of the patient[2,3,58]. Within 2 weeks of starting oral zinc 2 mg/Kg/day, the dermatitis clears and new hair grows[4].

Acne vulgaris

Several recent investigations demonstrated low zinc levels in acne vulgaris cases and the treatment with oral zinc, 220 mg three time per day for three months resulted in a significant improvement of papules, pustules and infiltrates[5-8]. No major untoward effects were noted during such therapy except for mild gastrointestinal symptoms in the form of nausea and vomiting with oral zinc therapy (Fig. 2).

Wound healing and leg ulcers

Pories et al[59] reported rapid wound healing (43% sooner) with oral zinc therapy of 220 mg three times a day.

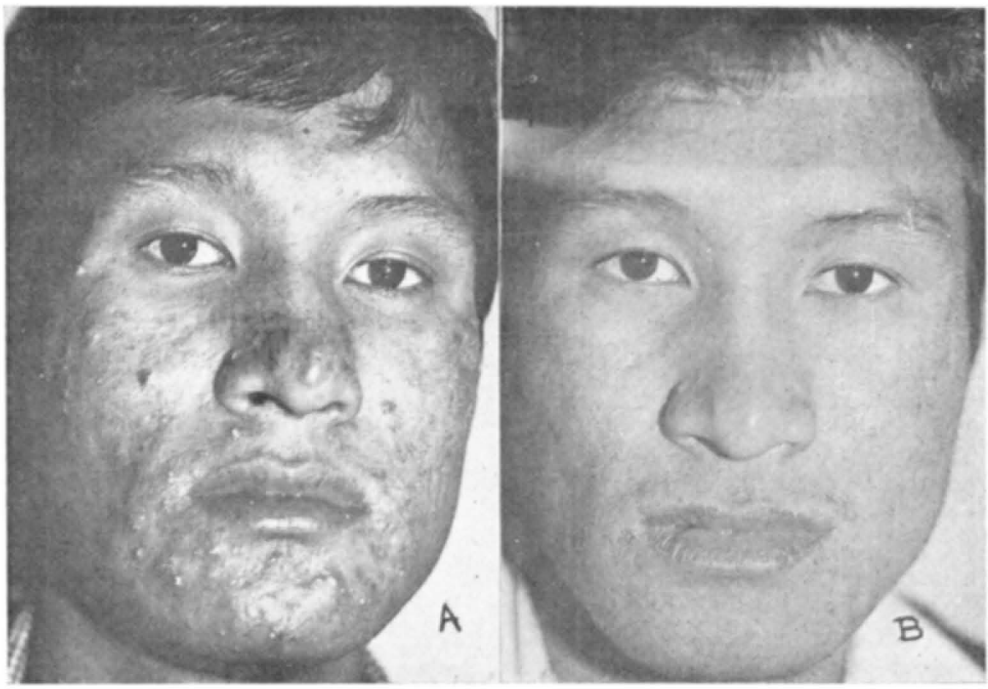

Fig. 2 Note the clinical improvement in acne before (A) and after (B) oral zinc therapy.

No toxic effects were noted during this study that continued for 61 days. Similarly, oral zinc was found to be useful in the treatment of chronic venous ulceration of legs[9].

Psoriasis

Portnoy and Molokhia[60] found normal serum zinc levels in psoriasis. In contrast to this, several other workers noted significantly low blood zinc levels in psoriasis as compared to matched controls[61-63]. Clemmensen et al[11] observed that oral zinc is valuable in the treatment of psoriatic arthritis. Reduction of joint pains and increase of mobility with decrease in the swelling were noted.

Pigmentary disorders

Markedly elevated zinc levels are known to occur in highly melanized structures like choroid of the eye[64], hair, pigmented moles and seborrheic warts [65]. Moreover, melanosomes, the melanin containing granules in melanocytes were found to contain large amounts of zinc[66]. The nature of association between zinc and melanin remains unexplored. It has been suggested that melanin may be acting as a potent chelating agent binding the zinc[67]. Molokhia and Portnoy[65] found that in vitiligo, there was a significant reduction in serum zinc while copper levels were increased in the hyperpigmented zone surrounding the lesion. Kader et al[69] also reported low zinc levels in the skin of vitiligo patients.

Rheumatoid arthritis

The serum zinc levels were reported to be lower in cases of rheumatoid arthritis as compared to normal controls[70]. Simkin[10] observed that oral zinc therapy was better than a placebo in the treatment of rheumatoid arthritis.

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