ZINC NUTRITIVE AND SKIN: AN OVERVIEW

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Summary

Zinc is an essential trace element which participates in several biochemical pathways. It is also important for skin homeostasis, as shown by the relevant changes of skin and its appendages during the primary form of zinc deficiency, named "acrodermatitis enteropathica" (AE). Cutaneous lesions resembling AE may also develop owing to acquired zinc deficiency due to multiple causes: nutritional factors, alcoholism, malabsorption, liver cirrhosis, chronic renal diseases and other chronic debilitating disorders. In acute zinc deficiency, the skin eruption is vesico-bullous or eczematous, whereas in the chronic state parakeratotic psoriasiform lesions occur. Other signs include widespread asteatotic eczema, cheilitis, glossitis, stomatitis, alopecia, nail anomalies, and are usually associated with extra-cutaneous manifestations. The recognition of the underlying zinc deficiency is of crucial value as zinc supplementation causes regression of symptoms.
In some skin disorders, the epidermal and/or serum concentrations of zinc were found to be decreased, but the actual implications of such abnormalities are still unknown and controversial, at least for some diseases. Some evidences seem to support the implication of zinc in wound healing, prevention of UVA-induced apoptosis, sebum composition and excretion. Some reports showed a potential usefulness of oral zinc in skin diseases, such as acne vulgaris, recalcitrant warts, leprosy, decubital ulcers, amicrobial pustulosis, erosive pustulosis of the scalp, perifolliculitis capitis abscedens et suffodiens and necrolytic acral erythema.

Riassunto

Lo zinco è un oligoelemento essenziale che prende parte a numerosi processi biochimici. Esso è anche di fondamentale importanza per l'omeostasi cutanea, come è dimostrato indirettamente dal coinvolgimento della cute e dei suoi annessi durante il deficit primitivo noto come "acrodermatite enteropatica" (AE). Lesioni simili a quelle dell'AE si possono osservare in caso di deficit acquisito di zinco secondario a patologie di vario tipo: carenze nutrizionali, alcolismo, malassorbimento, cirrosi epatica, nefropatie croniche e altre malattie debilitanti croniche. In corso di deficit acuto di zinco, le lesioni cutanee assumono un aspetto vescico-bolloso o eczematoso, mentre durante gli stadi cronici si notano prevalentemente manifestazioni psoriasiformi. Altri possibili segni sono eczema asteatosico, cheilite, glossite, stomatite, alopecia, onicodistrofie, e vari sintomi extra-cutanei. L'individuazione del deficit di zinco è fondamentale in questi casi dal momento che la terapia con zinco orale consente la regressione completa di tutti i sintomi.

In alcuni disordini cutanei si è riscontrata una riduzione delle concentrazioni epidermiche e/o sieriche di zinco, ma la reale rilevanza di tale riduzione è ancora sconosciuta, per lo meno in alcune condizioni. Si è ipotizzato un ruolo dello zinco nel processo di guarigione delle ferite, nella prevenzione dell'apoptosi indotta dagli UVA, nella composizione ed escrezione di sebo. Alcune esperienze depongono per il potenziale valore terapeutico dello zinco in talune dermopatie, come acne, verruche, lebbra, ulcere da decubito, pustolosi amicrobica, pustolosi erosiva del cuoio capelluto, perifolliculitis capitis abscedens et suffodiens ed eritema necrolitico acrale.

INTRODUCTION

Zinc is an essential trace element, contained at high concentrations in shellfish, legumes, nuts, whole grain and green leafy vegetables; fruits, wine, beer and spirits contain insignificant levels (1). Zinc supply depends on the protein content of the food; protein undernourishment and intake of foods with high amounts of phytates and fibres can lead to zinc deficiency. The daily oral dose of this element should be of approximately 3mg in infants less than 6 months, 5mg in infants 0.5 to 1 year old, 10mg in children 1 to 7 years old and 16mg from the 11th year onwards. During pregnancy and lactation, women should receive 20-25mg of zinc daily (2).

The normal serum level of zinc is about 70-125μg/100mg, equivalent to 11-19μmol/l. The mean concentration, determined by atomic absorption spectrophotometry, is about 60μg/g in epidermis and 40μg/g in upper dermis, with levels much higher in the upper than in the lower dermis layers (3).There is no correlation between the tissue and serum concentrations.

BIOLOGICAL FUNCTIONS

Basic functions

Zinc participates in several biochemical and biological pathways (Table I). In particular, it is well-known that several aspects of specific and non-specific immunity are regulated by zinc (4,5): development and functionality of neutrophils and NK cells; intracellular killing, cytokine production and phagocytosis of macrophages; many functions of T lymphocytes, including activation, Th1 cytokine production, B lymphocytes help; development of B lymphocytes and production of antibodies, especially of IgG. The effects of zinc on the immune system are mostly mediated by the influence on cellular functions (DNA replication, RNA transcription, cell division and activation). Furthermore zinc inhibits the production of tumor necrosis factor (6). Zinc is also a cofactor for over 200 enzymes (the most important of which are listed in Table II) (7-9). It is a constituent of some nuclear hormone receptors, such as those for steroids, thyroid hormones, vitamin D and retinoids (10).

Table I.
Principal biological functions regulated by zinc.

Immunity (both specific and non-specific)
DNA, RNA and protein synthesis
Cell division and activation
Action of several hormones and enzymes
Functional integrity of membranes
Growth
Development
Neurosensory functions
Apoptosis (inhibition)
Inflammation (inhibition)
Oxidative stress (inhibition)

Table II.
Principal enzymes with zinc-dependent activity.

Alkaline phosphatase
Alcohol dehydrogenase (and other dehydrogenases)
Carboxypeptidase
Digestive enzymes
Metalloproteinases
Thymulin
Thymopoietin
Cu-Zn superoxide dismutase
DNA and RNA polymerases
Thymidine kinase
Ribonuclease

Cutaneous functions

Zinc is also important for skin homeostasis; some evidences support its role for specific skin-related processes.

In human skin fibroblasts the antioxidant effects of zinc have been demonstrated; interestingly, these effects do not appear to be mediated by antioxidant metalloenzymes (11). It was also found that zinc can protect human cutaneous fi-

broblasts against both UVA1-induced DNA damage and early/delayed apoptosis (12).
The involvement in wound healing has been also suggested. During the healing process, zinc accumulates into the skin (13). Moreover, zinc supplementation leads to an higher percentage of Langerhans' cells having dendrites in the epidermis of patients with decubital ulcers; it is likely that the increased motility of these cells may favour the healing process of the lesions (14). However, the actual value of zinc in wound therapy is still controversial (15).
Hints suggesting a potential role of zinc in skin desquamation have been provided. In fact, a 25 kDa chymotrypsin-like proteinase possibly involved in this process has been characterized in the stratum corneum; this enzyme can be inhibited by zinc ion and also by aprotinin and chymostatin (16). This finding can explain, at least in part, the squamous nature of lesions associated with chronic zinc deficiency.

ZINC DEFICIENCY

Zinc deficiency may be distinguished in primary and acquired forms (17). In turn, the primary forms can be linked to a specific defect of absorption (acrodermatitis enteropathica) or to insufficient nutrition (endemic nutritional zinc deficiency). The acquired zinc deficiency is a consequence of gastrointestinal tract disorders causing diarrhoea and malabsorption or of other diseases.

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE) is a rare disease probably inherited in an autosomal recessive fashion, which was identified in 1936 by Brandt (18) and further investigated in 1942 by Danbolt and Closs (19) who gave the name to the disease.
The link between the disease and zinc deficiency was first described by Moynahan in 1974 (20). In patients affected by AE the zinc absorption is low (2-3% compared with 27-65% in normal adults); the precise cause of this malabsorption is unknown. Probably, some cases of AE can be caused by a cellular defect in zinc metabolism rather than by a reduced absorption (21).
Clinical features. The onset of the disease is usually 4-6 weeks after weaning or can occur earlier if breast milk is not given. AE is typically characterized by vesicobullous lesions on hands, feet and periorificial areas and several systemic symptoms: irritability, photophobia, hair loss and thinning, diarrhoea, stunted growth, decreased resistance to infections and poor wound healing. Angular cheilitis is an important clinical feature which seems to be associated with the risk of relapse and needs usually more time to improve during treatment compared with other manifestations (22).
Microscopic findings. The histological findings related to the vesicobullous lesions consist in intraepidermal vacuolization and massive ballooning, with prominent epidermal necrosis and with no acantholysis. Bullous lesions seem to develop *ex novo* on unaffected areas and not on erythematous patchy lesions (23). Light and polarizing microscopy of the hair can display uneven diameter of the shafts, atypical trichorrhexis nodosa with stretched fractures, pseudomonilethrix, irregular pattern of alternating dark and bright bands (24).
Diagnosis and management. In AE the serum zinc level is significantly decreased. However, serum zinc values are not a good index of tissue zinc concentrations; in the serum, zinc is almost entirely bound to transport proteins, and its tissue availability may be regulated by multiple factors. There is a good correlation between depressed plasma zinc levels and low alkaline phosphatase activity (25).
Without proper management, the prognosis is poor and in the past a lethal outcome occurred within 4-5 years. Oral zinc supplementation, at the daily dose of 2mg/kg, induces a prompt regression of symptoms within 1 or 2 weeks. Pro-

longed therapy at least to adult age is necessary to prevent recurrence of manifestations. Anyway, a trend towards improvement with age is possible. During supplementation, it is mandatory to monitor the serum levels of zinc and copper and the immune functions in order to provide a proper dosage of zinc according to different stages. In fact, several evidences have shown that excessive zinc dosages induce low copper levels with subsequent impairment of immune function (21,26).

Endemic nutritional zinc deficiency

This form has been described in severely malnourished children, presenting with dwarfism and hypogonadism as the main symptoms (27). The deficiency is due to the peculiar diet of people from some underdeveloped countries, which consists mainly of unleavened whole grain bread with a high fibre and phytate content; secondarily, concomitant concausal factors may be represented by the habit of clay eating and frequent hookworm infestation.

Acquired zinc deficiency

Etiology. Zinc-depletion syndrome was first recognized in patients with AE-like cutaneous lesions after prolonged total parenteral nutrition for bowel disturbances (28,29). The syndrome can develop within 2-3 months in adult subjects who receive as little as 0.2 mg/day or 1.3% of the recommended allowance (30); if there is a concomitant abnormal bowel function, zinc depletion can occur earlier. Premature infants are particularly prone to develop zinc deficiency, because they have negligible zinc stores, undergo rapid growth and show an insufficient absorption compared to mature infants, or because they receive mother's milk which has an insufficient zinc content. However normal neonates or growing children can also require increased zinc supplementation. Other groups at risk are pregnant women, elderly people and malnourished subjects (5-9).

All the conditions that decrease zinc absorption or increase the metal loss from the gastrointestinal tract, skin or urine are able to induce a zinc deficiency due to the limited availability of rapidly exchangeable zinc pools in the body (5-9, 26, 31-38) (Table III).

Table III.
Most important pathological conditions with risk of zinc deficiency.

Alcoholism (alcoholic liver cirrhosis and pancreatitis)
Malabsorption
Artificial nutrition
Chronic diarrhoea
Intestinal by-pass (especially in patients with poor eating habits)
Extensive burns
HIV infection
Chronic renal diseases
Chronic debilitating disorders
Sickle cell anemia
Drugs: chelating agents (penicillamine), cimetidine, diuretics (ACE-inhibitors, thiazides, chlorthalidone) and chemotherapy (cisplatin, antileukemics)

Clinical features. The syndrome includes acute or chronic forms (17,39-41). In acute zinc deficiency cutaneous symptoms resemble AE. The skin eruption is vesico-bullous or eczematous, located on hands, feet, anogenital area and at periorificial level; typical flat bullae surrounded by red-brown erythema can develop on flexural finger creases and palms. There can be also paronychial inflammation and angular stomatitis with perioral lesions sparing the vermilion border. Necrotic and burn-like lesions can be seen, as well as oozing lesions on the heels of bedridden patients. Hair growth stops and there can be a diffuse thinning of the scalp hair, possibly leading to total alopecia within few weeks.

The patients with chronic zinc deficiency show psoriasis-like parakeratotic changes on areas subject to repeated pressure and trauma; the lesions are well-demarcated, thickened and of a

brownish colour. Other skin changes include: lichenification, moderate scaling, seborrhoeic dermatitis-like lesions on the face, flare-up of acne vulgaris, delayed wound healing. In cirrhotics a widespread asteatotic eczema can occur. The hair have a poor and sparse growth and show structural changes. White, transverse bands and depressions may be observed on the nails. In severe deficiency, deep transverse depressions (Beau's lines) on the finger nails due to temporary arrest of nail growth become visible 3-4 weeks after the start of zinc supplementation.

Various degrees of systemic involvement are possible (Table IV) depending on the severity of deficiency (8,9,40). Interestingly, diarrhoea is not only a cause of zinc deficiency but also a consequence of this through still unknown mechanisms.

Table IV.
Possible systemic symptoms of zinc deficiency.

Delayed puberty in adolescents
Diarrhoea
Emotional disorders
Growth retardation
Hyperammonemia
Impaired reproductive development in males (hypogonadism, oligospermia)
Intercurrent infections
Mental lethargy
Ocular abnormalities (reduced ability to dark adapt, photophobia, optic neuritis)
Poor appetite
Taste abnormalities
Weight loss

Diagnosis. The serum zinc and alkaline phosphatase levels are low (39); between these two parameters there is a positive correlation which can be used diagnostically and to control the effects of treatment. It is also important to consider the level of plasma albumin that binds 60-70% of circulating zinc. The actual utility of measuring zinc concentrations in hair and sweat is still uncertain. Skin changes related to acute and chronic zinc deficiency must be differentiated with a great variety of vesico bullous and scaly disorders, respectively. Differential diagnosis also includes eczematous eruptions, psoriasis, stasis eczema (42), asteatotic eczema, seborrhoeic eczema, kwashiorkor, pellagra and necrolytic migratory erythema (43,44).

Management. Severe forms can be fatal if unrecognized and untreated. Therapy in adult patients is based on oral zinc sulphate tablets of 0.2 g b.i.d or t.i.d. (about 2 mg zinc/kg); similar doses on a kilogram basis are given to children. Parenterally, 0,2-0,3 mg zinc/kg/day can be used in severe acute forms. During zinc therapy serum copper and immune status should be carefully monitored. Long-term high zinc supplementation is not recommended and is indicated only for AE (40).

ZINC AND SKIN DISEASES

The role of zinc in the pathogenesis of some skin diseases has been frequently claimed, although conclusive results are available only in some instances. There are several reports suggesting the therapeutic potential of zinc for skin-related disorders. Some of these reports are however anecdotical and need to be confirmed by controlled studies.

Leprosy

In several trials the zinc serum levels and the effects of oral zinc as an immunomodulator in leprosy were studied. In all subtypes, especially in erythema nodosum leprosum, low serum zinc levels with parallel increase of serum copper were observed. Zinc therapy restored normal zinc levels but was unable to reduce copper levels (45).

In subjects with multibacillary leprosy oral zinc was administered in combination with conventional antileprosy drugs. The addition of zinc induced faster clinical improvement, rapid fall in the bacterial index, greater influx of lymphocy-

tes in the granuloma and neovascularization (46). Moreover, the adjunctive therapy with zinc in recurrent erythema nodosum leprosum caused a marked improvement in the frequency, duration, and severity of the reaction, with a significant decrease of steroid requirement (47,48).

Allergic contact dermatitis to nickel

In a guinea pig model, without zinc sulphate interventions, nickel-exposure resulted in significantly higher stimulation indices at the lymphocyte transformation test as compared to non-exposed controls (49).
Weissmann and Menné (50) reported cases of nickel dermatitis improving after oral administration of zinc sulphate. The response to zinc sulphate has been more recently studied in 15 patients sensitized to nickel (51). Zinc improved both clinical manifestations and pruritus, and abolished or reduced the majority of patch test reactions. According to the authors of this study (51), several mechanisms of action of zinc can be speculated in nickel contact allergy, including: prevention of complete antigen formation, removal or decreased absorption of nickel, and reduction of reactive oxygen species.

Acne vulgaris

Rebello et al. (52) demonstrated an inibitory effect of zinc on the lipase of *Propionibacterium* species found in human pilosebaceous follicles. They noted also a small, but not significant, fall in the free fatty acid content of skin surface lipid *in vivo* in acne patients treated with zinc. Other authors pointed out that supplemental zinc sulphate may reduce the quantity of skin-surface sebum (53).
An *in vivo* study conducted in acne patients treated with zinc gluconate suggests that this treatment can inhibit chemotaxis of polymorphonuclear cells by reducing granulocyte zinc levels (54). Recent studies support the effectiveness of zinc gluconate for the treatment of inflammatory acne (55,56).

Miscellaneous disorders

There have been some evidences suggesting a potential usefulness of oral zinc supplement in the prevention of diaper rash in normal infants (57), but this topic has not been further investigated.
In some skin disorders such as acne, psoriasis, dermatitis herpetiformis and Darier's disease, the zinc epidermal concentrations were found to be decreased, in spite of normal serum zinc levels, but the actual implications of such abnormalities are still unknown and may be non-specific (58).
Low serum zinc was also observed in children with atopic eczema; it was suspected that this finding could be regarded as a non-specific consequence of the dermatitis and that there was no indication for zinc therapy in patients with atopic eczema (59). This was subsequently confirmed by a double-blind placebo-controlled trial which demonstrated no improvement of disease activity by zinc sulphate (60).
Beneton and coworkers (61) described two young women with amicrobial pustulosis associated with autoimmune diseases, in whom the pustulosis healed with zinc supplementation. Oral administration of zinc is also considered effective for the treatment of erosive pustular dermatitis of the scalp (62,63), perifolliculitis capitis abscedens et suffodiens (64) and necrolytic acral erythema (65).
A recent placebo-controlled trial (66) has highlighted the efficacy and safety of oral zinc sulphate in the treatment of recalcitrant warts. In fact, in the zinc-treated group a complete clearance was observed in about 61% of cases after 1 month and 87% of cases after 2 months of treatment with 10mg/kg daily. A direct relationship between response to treatment and serum zinc level was observed.
Nutritional factors have been implicated in the

precipitation of systemic lupus erythematosus (SLE); among the aggravating substances, some authors include excess calories and protein, high fat, iron, L-canavanine and zinc (67). In 1979 Fjellner (68) described the case of a woman, treated with hydralazine and propranolol for 6 years, who developed multisystemic manifestations of a LE-like syndrome within one week after starting oral zinc therapy. The actual role of zinc as inducer of SLE is still obscure, although some evidences suggest the involvement of zinc in both the functionality of some autoantigens and in the activity of enzymes operating in some autoimmune reactions (69,70).

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