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Physiological role of zinc

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Zinc is essential for normal life in animals and man and appears to play an important role in a large number of biological processes. Body zinc content appears to be under close homeostatic control by regulation of the processes of both zinc absorption and excretion. No substantial store of zinc appears to exist in man and little of the total body zinc appears to be available for redistribution to prevent the onset of zinc-deficiency symptoms. However, a clear appreciation of the role of this element in human pathology is still lacking. The major reason for this is a lack of accepted techniques for the assessment of the small 'mobile' pools which are important in the maintenance of critical poorly-understood Zn-dependent processes which when disturbed lead to the clinical manifestations of zinc deficiency.

INTRODUCTION

Zinc was first recognised to be essential for normal growth in animals in the 1930s (Todd *et al.*, 1934; Bertrand & Bhattacherjee, 1935) and a firm biochemical role for the element was first described in the 1940s (Keilin & Mann, 1944). However a clear appreciation of the role of this element in human pathology is still lacking, the major reason for this being a lack of appropriate techniques for the accurate assessment of body zinc status and a lack of knowledge concerning the key sites for zinc's metabolic actions in the body (i.e. important zinc 'pools') which when depleted or disturbed lead to clinical manifestations of zinc deficiency.

The aim of this review is to discuss briefly the known pathological effects and disorders where zinc appears to play a role, the key biochemical roles which the element plays in human metabolism and the sophisticated mechanisms which the body has developed for the maintenance of body zinc content. Throughout the review the authors will attempt to indicate areas where knowledge is sparse and further work is required in order to assist further development of this challenging field. A number of key areas of zinc metabolism will not be addressed in this paper, including the role of zinc in cell division, immunocompetence, behaviour and zinc toxicity; for a review of these areas readers are encouraged to consult the recent excellent book edited by Mills (1989).

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ZINC IN HUMAN PATHOLOGY

Prior to 1974 discussion of the involvement of zinc in human pathology centred around three areas: hypogonadal dwarfism in certain underdeveloped rural communities, a role in wound healing and a role in sensory abnormalities.

Hypogonadal dwarfism

Prasad and co-workers (1961) described a group of 18- to 20-year-old Iranian males with iron deficiency anaemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. They suggested that the cause of this syndrome was zinc deficiency and that ingestion of clay, which was prevalent in that area was chelating both iron and zinc, preventing their absorption. Prasad and co-workers also described a similar group of Egyptian males who had parasitic infections but no geophagia and in this group studies with ^{65}Zn apparently demonstrated an abnormal turnover of the element (Prasad *et al.*, 1963). These subjects also had reduced concentrations of zinc in their plasma, hair and sweat.

Apparent confirmation of the role of zinc in this disorder was provided by two zinc supplementation studies in Iran (Halstead *et al.*, 1972) and Egypt (Sandstead *et al.*, 1967) where beneficial effects were seen, but studies by Coble and co-workers (1966*a*,*b*) have cast doubt on the original findings. Coble and co-workers re-examined the Egyptian subjects studied by Prasad's group three and a half years after the original study and found that the subjects had matured

sexually and attained a stature comparable to adult Egyptian villagers, but their plasma zinc levels were still low. They also described similar groups of subjects fitting the criteria of hypogonadal dwarfs with low plasma zinc contents *and* groups of young local inhabitants with normal growth and development, but with comparably low plasma zinc concentrations.

These data are therefore contradictory in terms of a primary role for zinc deficiency in this complex syndrome. It seems likely that the combination of geophagia and/or parasitic infections together with marginal diets rich in fibre and phytate may contribute to a reduced zinc status in all subjects in these and many other underdeveloped rural populations (Prasad, 1988), but other nutritional deficiencies are also likely to occur in such communities. Therefore thirty years after the first suggestion of an involvement of zinc in this syndrome the situation is still not clear and only the future availability of novel techniques for assessing zinc status is likely to clarify the problem finally.

Zinc and wound healing

Pories and co-workers (1967) reported an apparent increase in healing rate following pilonoidal cyst excision in young airmen receiving 150 mg of zinc supplements per day. These data could not be confirmed by other workers and subsequently have become the subject of much controversy (see Sunderman, 1975 for a review). Zinc has also been claimed to be beneficial for the healing of ulcers of various different kinds, but again an unequivocal demonstration of a beneficial effect in zinc-replete subjects has not been shown (see Solomons *et al.*, 1988, for a review).

Zinc and sensory abnormalities

An association between trace metal deficiency and hypogeusia was first reported by Henkin *et al.* (1967) in describing beneficial effects of copper supplements in patients with hypogeusia following penicillamine therapy. Henkin and co-workers subsequently extended this work to demonstrate beneficial effects of zinc and other trace elements on both hypogeusia and hyposmia (Henkin & Bradley, 1970; Schechter *et al.*, 1972). Again this work has become the object of considerable controversy with serious criticisms being raised of the manner in which these original studies were undertaken (Culliton, 1975). Nevertheless, completely independent groups have reported hypogeusia in conditions where zinc deficiency may be present (Hambidge *et al.*, 1972; O'Nion *et al.*, 1978). Consequently another long-standing controversy concerning zinc and human pathology is still not resolved.

It is therefore apparent that the role of zinc in the three pathological areas so far described is very ambiguous and whether zinc had a clearly defined role in human pathology was in doubt until 1974 when it was recognised that acrodermatitis enteropathica was clearly related to a disturbance in zinc metabolism (Moynahan, 1974).

Acrodermatitis enteropathica

Moynahan's realisation that this disorder is treatable with small oral doses of zinc and associated with zinc deficiency is a clear watershed in studies of zinc pathology and metabolism in man. Although it is now recognised that the symptoms in the untreated disorder reflect a severely zinc-depleted state and that milder forms of zinc deficiency can occur in man, the discovery provided a unique 'window' into zinc metabolism and such a stimulus to research in this field that much of our current knowledge of zinc can be attributed directly or indirectly to this.

The disorder was first described by Danbolt and Closs (1942) and is an autosomal recessive disorder characterised by severe diarrhoea, dermatitis and alopecia beginning in infancy coincident with the change from breast milk to cows' milk. Acrodermatitis enteropathica was inevitably fatal until 1953 when Dillaha *et al.* (1953) found that oral treatment with di-iodohydroxyquinoline (diodoquin) produced rapid improvement of symptoms.

Barnes and Moynahan (1973) initially described a patient who was thought to suffer from a variant of the disease in which lactose intolerance was also present and who was treated with diodoquin and a synthetic lactose-free diet with no benefit. Analysis of the synthetic diet revealed that it was deficient in zinc and molybdenum and further investigation revealed a low plasma zinc content in the patient. The patient rapidly recovered on zinc supplements and Moynahan, realising that the clinical symptoms of acrodermatitis enteropathica were very similar to those of experimental zinc deficiency in animals began a therapeutic trial of zinc supplements in ten other patients with the disorder. A complete remission of symptoms was obtained in all patients treated with zinc (Moynahan, 1974) which was rapidly confirmed in other laboratories (Michaelson, 1974; Thyreson, 1974; Nelder & Hambidge, 1975). All cases were also found to have low plasma zinc concentrations which were corrected by oral zinc supplements, but not by diodoquin therapy.

Acrodermatitis enteropathica is therefore a true zinc deficiency disorder and it appears extremely likely, although it is not yet proven, that it is due to a genetic defect in gastrointestinal zinc absorptive mechanisms (Lombeck *et al.*, 1975; Aggett *et al.*, 1978). Small oral zinc supplements appear to provide complete remission of symptoms in the disorder and restore a normal morbidity and mortality to the individuals. Interestingly, limited data suggested that pregnancy in untreated or diodoquin-treated patients with this disorder was

associated with an increased risk of congenital malformations in the offspring, but this also appears to be negated by zinc therapy (Brenton *et al.*, 1981).

Other pathologies

Consideration of the clinical symptoms of acrodermatitis enteropathica by other workers rapidly led to the recognition of an involvement of zinc in other pathological conditions: the dermatological symptoms associated with long-term total parenteral nutrition were found to respond to zinc supplements (Arakawa *et al.*, 1976; Kay *et al.*, 1976) while others described similar changes in certain patients suffering from a generalised malabsorption defect (Weisman *et al.*, 1978). Golden and Golden (1979; 1981) recognised a crucial role for zinc deficiency as a severe complicating factor in protein-calorie malnutrition, particularly following initiation of therapeutic regimes containing high energy protein content, but low zinc. These studies have dramatically demonstrated the requirement of zinc for growth and have led to fundamental changes in the management of such patients. Severe zinc deficiency as a consequence of chelating agent therapy has also been described, most dramatically following therapy with diethylene triamine pentacetic acid in a patient with iron overload due to blood transfusion for thalassaemia major (Jackson *et al.*, 1983).

It is now recognised that there are a number of general situations where zinc deficiency can occur (Table 1) although unless present in a severe form it can be difficult to diagnose and may be of debatable importance. A more complete discussion of the possible role which moderate or mild zinc deficiency may play in human pathology is provided by Hambidge (1988), but a full recognition of the importance of marginally low zinc status will not be possible until improved methods of assessing zinc status in populations become available.

ZINC IN TISSUES

Zinc in tissues appears to be primarily present in a protein-bound form (Cousins, 1985). It is an essential part of a large number of metalloenzymes, appears to act as a regulator of a small number of enzyme systems (Williams, 1988) and is essential for the normal function of a number of proteins influencing/regulating transcription of genes. In these regulatory proteins the peptide chains are arranged in a characteristic repeating loop shape with zinc complexed to amino acids across the base of the loop; these are known as 'zinc finger' proteins (Chesters, 1991).

Table 1. General situations where zinc deficiency may occur

1. Dietary deficiency:	e.g.—Protein calorie malnutrition
	—Synthetic diets
	—i.v. feeding
	—Underdeveloped rural communities
2. Malabsorption syndromes:	e.g.—Acrodermatitis enteropathica
	—Non-specific malabsorption (Coelic, Crohn's disease)
3. Increased body losses:	e.g.—Chelating agent therapy
	—Chronic diarrhoea
4. Abnormal zinc metabolism:	e.g.—Alcoholic liver disease (?)

The role of disturbances of any of these zinc-dependent systems in the pathology of zinc deficiency is not clear. Zinc deficiency of a sufficient severity to cause clinical changes leads to only minor variations in the content of zinc in some tissues and no change in many others (Jackson *et al.*, 1982). Thus rats with loss of hair and parakeratotic lesions of the skin due to dietary zinc depletion have no detectable changes in the zinc content of either hair or skin (Jackson *et al.*, 1982) and a patient with severe stasis eczema associated with zinc deficiency and corrected by zinc supplements had a normal dermal zinc content (Jackson *et al.*, 1982). It is therefore apparent that the activity of most zinc-dependent enzymes in tissue will be unaffected by zinc deficiency since the total zinc content is not reduced. Insufficient data are currently available to determine whether 'zinc finger' proteins are affected by dietary zinc depletion, although preliminary data suggest that they are not (Chesters, 1991).

The majority (>90%) of the total body zinc (1–2 g in man) is present within tissues (Jackson, 1988) and it is apparent that very little of this zinc is freely exchangeable and available to other sites during times of depletion. There is therefore no substantial store of zinc within the body to act as a buffer against a lack of zinc in the diet. Nevertheless, man appears to be able to cope with wide variations in the dietary intake of zinc (and in the composition of the diet) to prevent the onset of zinc deficiency. This appears to have been achieved by the development of complex mechanisms to maintain whole body homeostasis.

HOMEOSTASIS MECHANISMS

Zinc in the diet is ingested in association with a number of other factors which may either promote or antagonise zinc absorption (Table 2). Particularly important in this respect appears to be phytate which is present in many unrefined foods and present at high concentrations in many diets in certain undeveloped rural populations. In addition the absolute content of zinc in the diet can vary to a large extent (Sandstrom, 1988). The body has therefore the task of maintaining body zinc supply in the presence of potentially large variations in the amount of zinc available for absorption without a substantial store of body zinc to act as a 'buffer'. Its primary means of achieving this is by

Table 2. Potential dietary promoters and antagonists of zinc absorption

Antagonists	Promotors
Phytate	Histidine
High fibre foods	Animal protein
Hemicellulose	Congeners in red wine
Oxalate	
Calcium	
Iron	
Copper	
Tin	

Derived from Sandstrom & Lonnerdal (1988) and Fairweather-Tait (1988).

variation in both the amount (fraction) of zinc absorbed and the amount excreted from the body (Cotzias *et al.*, 1962; Miller, 1969; Jackson *et al.*, 1984).

The ability of man to maintain balance for zinc over a wide range of dietary intakes is shown in Fig. 1. These data are derived from various studies where normal subjects have been allowed to adapt to the diet on which they were studied and essentially the data demonstrate that subjects can maintain zinc balance at dietary zinc contents above about 4–5 mg/day. It should be noted that these studies were all undertaken under experimental conditions and the availability of the dietary zinc for absorption is likely to be high.

Evidence of the way such adaptations occur is shown by the data in Table 3 (derived from King and Turnlund, 1988) showing the changes in zinc

Table 3. Effect of dietary zinc content on zinc absorption and endogenous loss (mg/d)

Dietary zinc	4·6–4·5	7·4–11·5	13·0–16·8	19
Zinc absorption	2·9 (±0·2)	2·6 (±0·2)	4·4 (±0·7)	4·4
Endogenous loss	2·3 (±0·2)	2·2 (±0·3)	3·8 (±0·9)	4·1

Derived from King & Turnlund, 1988.

absorption and endogenous excretion which occur in response to changes in the dietary zinc content in normal subjects. Even more dramatic effects have been described in one normal subject in whom the dietary zinc content was varied in a stepwise manner (Jackson *et al.*, 1984) and a population of malnourished lactating women in Brazil was found to have zinc absorption rates approaching 80% of the dietary intake (Jackson *et al.*, 1988).

Little zinc is excreted in the urine and therefore changes in the urine zinc content cannot contribute significantly to the maintenance of whole body homeostasis and normal intakes, although the urinary zinc content does fall during overt depletion of zinc (Nelder & Hambidge, 1975).

Although a substantial number of descriptive studies of these processes have been undertaken very little is known about the mechanisms by which zinc absorption, excretion and generalised membrane transport occur. It is clear that there is a relatively specific mechanism for the transfer of zinc from the small intestinal lumen to the body and where studies of the kinetics of

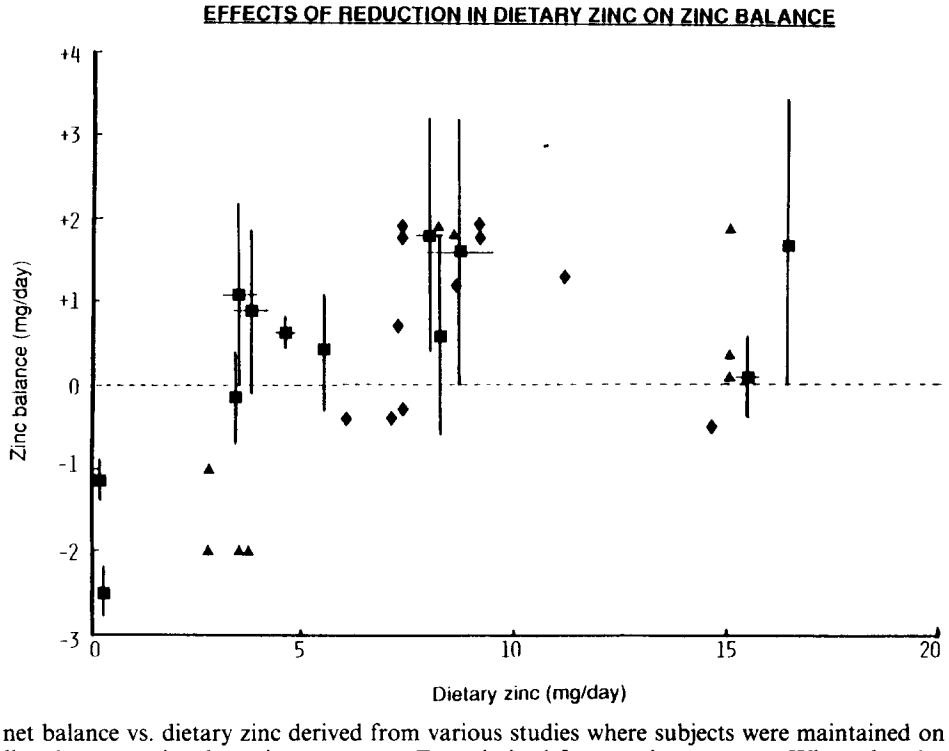

Fig. 1. A plot of net balance vs. dietary zinc derived from various studies where subjects were maintained on diets for lengths of time sufficient to allow homeostatic adaptations to occur. Data derived from various sources. Where data have been reported as individual results these are presented separately, where means and standard deviations were reported these are represented by error bars.

absorption have been undertaken it is clear that zinc transport occurs (at least in part) by carrier-mediated kinetics (Davies, 1980; Menard & Cousins, 1983; Raffaniello & Wapnir, 1989). However, little progress has been made in the identification of zinc transporter proteins in the mucosa. Where workers have attempted to identify ^{65}Zn-binding proteins from the small intestine by column chromatography (Kowarski *et al.*, 1974; Hurley *et al.*, 1977) many mucosal proteins have been found to bind ^{65}Zn and no specific transport proteins have been identified. It is therefore clear that further refinement of this type of approach is unlikely to produce useful data and novel approaches are required to obtain this important information.

ASSESSMENT OF ZINC STATUS

Reference has been made throughout this review to the problem of assessment of zinc status. This problem has been reviewed by Solomons (1979) and by Golden (1988). It is apparent that the plasma zinc concentration is the most widely used indicator, but plasma zinc concentrations are known to fall due to stresses such as post-operative or endotoxin stress unassociated with zinc deficiency (Hallbrook & Hedelin, 1977) and no readily accessible tissues are suitable indicators of body zinc status (Jackson *et al.*, 1982). New reliable indicators of status are therefore required. We have attempted to address this problem by measurement of zinc 'pool' sizes and rates of zinc turnover using isotopic techniques. Initial results (Lowe *et al.*, 1991) suggest that use of kinetic techniques can provide information on the size and turnover of an intracellular 'pool', primarily located within the liver, which appears to fall reproducibly during zinc depletion. Kinetic methods, although time-consuming and costly, may therefore offer an answer to this problem under certain circumstances.

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