

## Zinc metabolism in thyroid disease

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### Summary

This study was designed to evaluate the zinc metabolism in adults of both sexes with thyroid disease. Plasma and erythrocyte zinc concentration and urinary zinc excretion were investigated. The mean concentration of plasma zinc in hypothyroid patients and in euthyroid patients, previously either hyperthyroid or hypothyroid, was lower than that of control subjects, whereas no statistically significant differences were observed in plasma zinc values between hyperthyroid patients and control subjects. The average erythrocyte zinc level in patients with thyroid disease was significantly lower than that in control subjects. Erythrocyte zinc concentration was significantly decreased in hyperthyroidism compared with hypothyroidism, or patients previously either hyperthyroid or hypothyroid but now euthyroid. Increased urinary zinc excretion in hyperthyroidism was noticed compared to euthyroid and hypothyroid patients and to control subjects. Increased urinary zinc concentrations may result from increased tissue catabolism such as muscle. The results of this study suggest that abnormal zinc metabolism occurs commonly in patients with thyroid disease.

### Introduction

Trace elements are known to influence hormones at several levels of action, including hormone secretion and activity and binding to target tissue. Conversely, hormones influence trace metal metabolism at several levels of action, including excretion and transport of trace metals (Henkin, 1976). Trace metals which have been observed to affect the endocrine system adversely because of their deficiency have been zinc, copper and manganese. Their effects are usually produced through decreased dietary intake or increased body loss of the metals (Henkin, 1976). Despite widespread interest in hyperzincuria as an indicator of catabolism, little

information has been available on zinc status in thyroid disease. The present study was undertaken to investigate the concentration of zinc in plasma and erythrocyte, and urinary zinc excretion in patients with thyroid disease. Red cell zinc concentrations are easy to study and reflect the chronic status of zinc in the body (Prasad, Abbasi and Ortega, 1977).

### Materials and methods

Patients with thyroid disease aged 18 to 56 years and healthy subjects aged 21 to 48 years took part in this study. On the basis of the clinical picture and thyroid function tests, including serum thyroxine level, serum triiodothyronine level, serum TSH level, or thyroid uptake of <sup>131</sup>I, 37 had overt hyperthyroidism, 32 previously hyperthyroid were now euthyroid, 10 had overt hypothyroidism and 21 previously hypothyroid were now euthyroid. Anti-thyroid drugs were used in the treatment of hyperthyroidism and synthetic thyroid hormones in hypothyroidism. None of the subjects studied had either proteinuria or glucosuria.

Blood from fasting subjects was drawn in the morning into a heparinized disposable plastic syringe with a stainless steel disposable needle. Twenty-four-hr specimens of urine were collected in an acid-cleaned plastic container. Blood samples were centrifuged at 3000 rev/min for 10 min and plasma samples with apparent haemolysis were discarded. The buffy coat, containing white blood cells and platelets, was then removed by aspiration. The sedimented erythrocytes were washed 3 times in isotonic saline and packed erythrocytes were obtained. The haemoglobin was read at 541 nm in a spectrophotometer.

A simple procedure of dilution and direct aspiration was employed. Plasma and red blood cells were prepared by dilution with de-ionized distilled water; plasma in a dilution of 1 to 4 and packed red

blood cells by lysing the cells and diluting 1 to 29. Urine was aspirated directly without dilution. In all instances the zinc determinations were performed in duplicate using an atomic absorption spectrophotometer. De-ionized distilled water, saline and acid-washed instruments were all free of zinc.

Results were expressed as  $\mu\text{g}$  of zinc per dl of plasma; as  $\mu\text{g}$  per g of haemoglobin of erythrocyte; or as  $\mu\text{g}$  per 24-hr of urine.

**Results**

*Plasma zinc concentration*

Relevant data for subjects grouped according to thyroid status are shown in Fig. 1. No statistically significant differences were found in plasma zinc concentrations between patients with hyperthyroidism and control subjects, or between those with untreated hyperthyroidism and those with hyperthyroidism on treatment. The mean concentration of plasma zinc in patients previously hyperthyroid but now euthyroid was significantly lower than that for control subjects ( $P < 0.01$ ) and that for patients with hyperthyroidism ( $P < 0.05$ ).

The mean concentration of plasma zinc was found to be lower in hypothyroid patients and in patients previously hypothyroid but now euthyroid when compared with control subjects. There were no significant differences between hypothyroid patients

and patients previously hypothyroid but now euthyroid.

*Erythrocyte zinc concentration*

As shown in Fig. 2, the mean concentration of zinc in patients with thyroid disease was significantly lower than that in control subjects. Erythrocyte zinc concentrations were significantly lower in thyrotoxic patients compared with patients previously hyperthyroid but now euthyroid ( $P < 0.001$ ). There were, however, no significant differences between untreated hyperthyroidism and thyrotoxic patients on treatment. None of the thyrotoxic patients had normal erythrocyte zinc values and only 3 euthyroid patients, previously hyperthyroid off treatment, had normal erythrocyte zinc values.

The zinc content of erythrocytes in hypothyroid patients and in patients previously hypothyroid but now euthyroid was significantly lower than that in control subjects, but higher than that in hyperthyroid patients. Erythrocyte zinc concentrations in 7 of 21 patients previously hypothyroid but now euthyroid and 2 of 10 hypothyroid patients were within normal limits.

*Urinary zinc excretion*

This study demonstrated a significantly higher

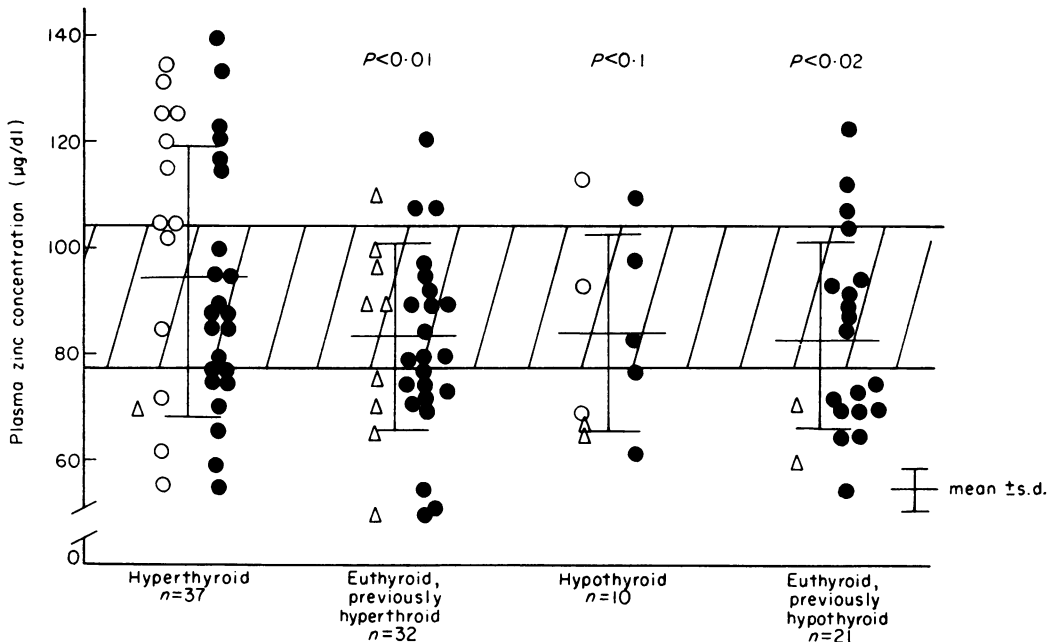


FIG. 1. Plasma zinc concentration in sub-grouped patients with thyroid disease as compared to healthy adults. Shaded area indicates the range for healthy adults (mean  $\pm$  s.d.) P values compared to healthy adults.  $\circ$ , untreated;  $\bullet$ , on treatment;  $\triangle$ , off treatment.

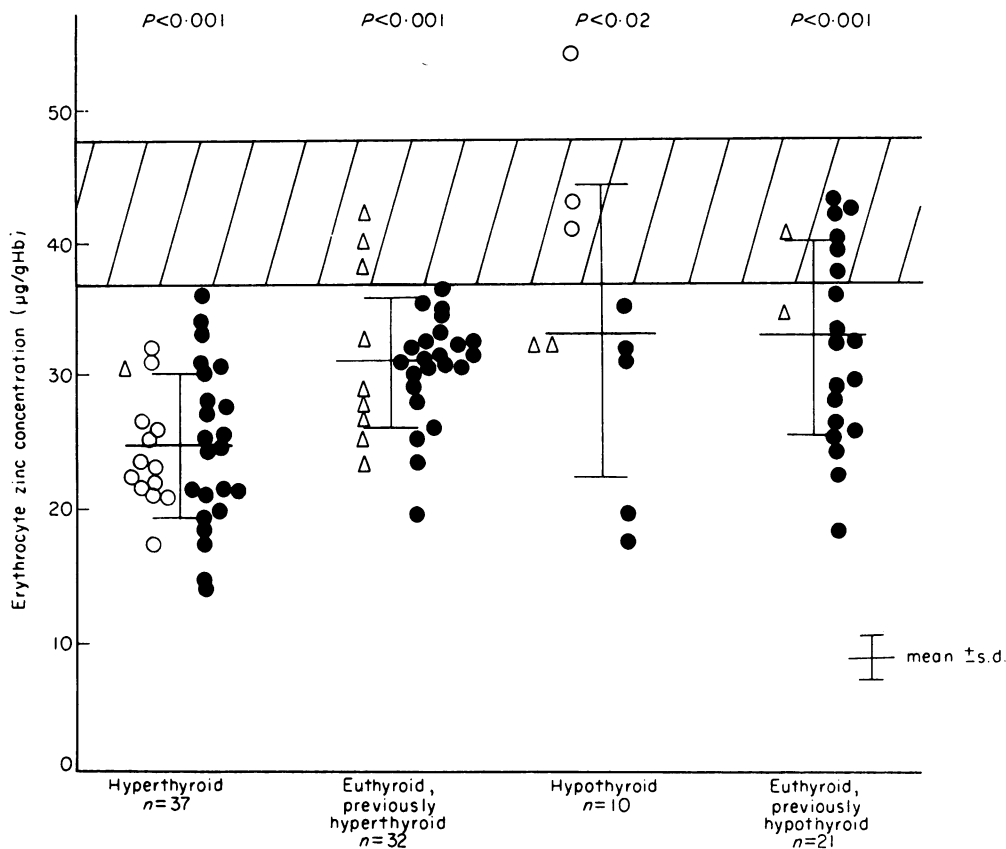


FIG. 2. Erythrocyte zinc concentration in sub-grouped patients with thyroid disease as compared to healthy patients. Shaded area indicates the range for healthy adults (mean  $\pm$  s.d.)  $P$  values compared to healthy adults.  $\circ$ , untreated;  $\bullet$ , on treatment;  $\Delta$ , off treatment.

urinary zinc excretion in thyrotoxic patients compared with euthyroid and hypothyroid patients as well as control subjects (Fig. 3). However, no statistically significant differences were observed between the values for patients previously either hyperthyroid or hypothyroid and now euthyroid and those for control subjects. Slightly increased, but not statistically significant, urinary excretion of zinc occurred in patients previously hypothyroid and now euthyroid.

### Discussion

The present study showed differences in plasma and erythrocyte zinc concentrations, and urinary zinc excretion in patients with thyroid disease. Reports on zinc metabolism in patients with thyroid disease are few. Higher zinc values in serum were reported in hyperthyroidism (Wolff, 1956). However Bremner and Fell (1977) showed that plasma zinc concentrations in hyperthyroidism or in hypo-

thyroidism were not different from those of healthy subjects. The present results on plasma zinc concentration in patients with overt hyperthyroidism demonstrated a similar pattern to that reported by Bremner and Fell (1977). In contrast, however, this study indicates that plasma zinc concentrations in hypothyroid patients and in euthyroid patients, previously either hyperthyroid or hypothyroid, were significantly lower than those of control subjects and those of thyrotoxic patients.

Plasma zinc concentration does not always reflect the total body zinc status. Even in zinc-deficient patients the plasma zinc concentration may be normal. The corollary is also true in that hypozincaemia, such as that noted during acute infections and hypoproteinaemic states, and in women in late pregnancy and when taking oral contraceptives, may not reflect true zinc deficiency (Hambidge, 1977; Underwood, 1977).

The measurement of erythrocyte zinc content

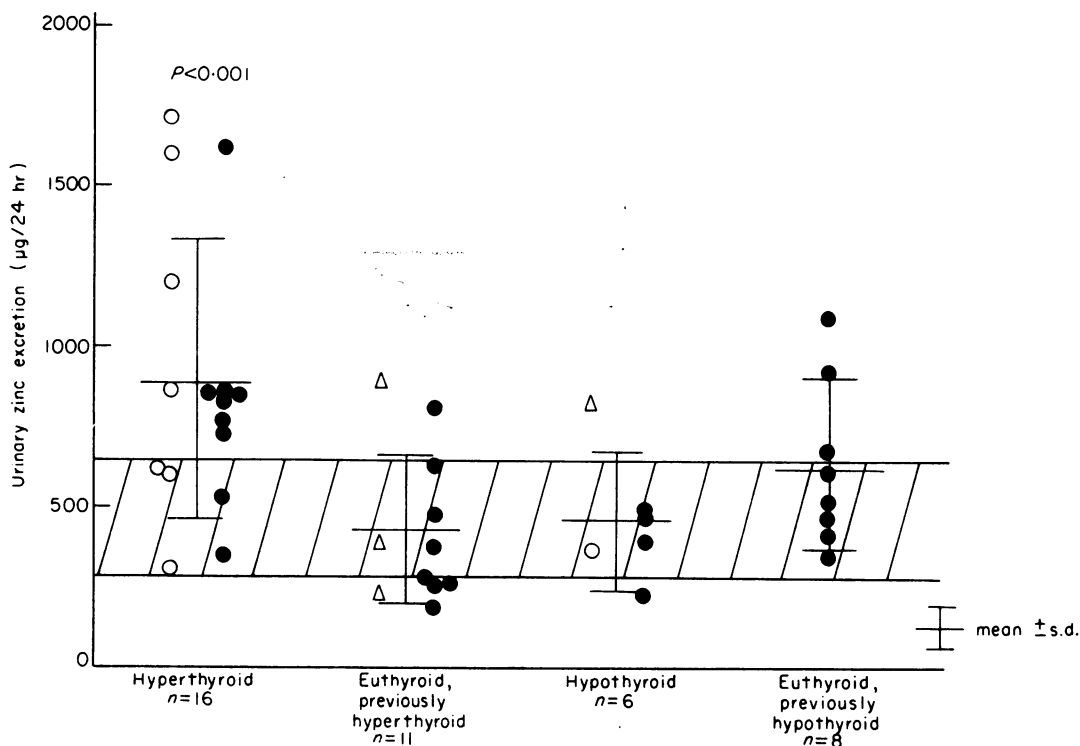


FIG. 3. Urinary zinc excretion in sub-grouped patients with thyroid disease as compared to healthy adults. Shaded area indicate the range for healthy adults (mean  $\pm$  s.d.)  $P$  values compared to healthy adults.  $\circ$ , untreated;  $\bullet$ , on treatment;  $\triangle$ , off treatment.

appears to be another useful indicator for assessing zinc nutritional status. However, little information is available on red blood cell zinc concentration in thyroid disease.

Pangaro *et al.* (1974) demonstrated that erythrocyte zinc concentrations in hyperthyroidism were significantly lower than those in control subjects. The present study confirms these findings that red blood cell zinc concentration is decreased in patients with thyroid disease. Both zinc and carbonic anhydrase, which is by far the most abundant zinc metalloenzyme in erythrocytes, were decreased in hyperthyroidism (Pangaro *et al.*, 1974; Seino *et al.*, 1976). This finding was considered to be possibly a specific action of thyroid hormones on carbonic anhydrase in erythrocytes. Moreover, exogenous thyroid hormones may also influence zinc metabolism, since patients with untreated hypothyroidism had a normal or rather higher zinc content of erythrocyte, but those with hypothyroidism on treatment and patients previously hypothyroid but now euthyroid had a lower erythrocyte zinc concentration.

The present investigation has shown a significantly higher zinc output in urine in thyrotoxic patients compared with euthyroid and hypothyroid patients and with control subjects, a similar pattern to that

reported by Bremner and Fell (1977). Higher urinary zinc excretion may result from an increased extracellular fluid zinc loss, but is not a renal phenomenon because of the increased zinc clearance and the increased ratio of zinc clearance:creatinine clearance in thyrotoxic patients (Bremner and Fell, 1977). Plasma zinc concentrations were maintained within normal limits in thyrotoxic patients despite the increased urinary losses; this may reflect the mobilization of zinc from tissue such as erythrocyte, bone and muscle by increased catabolism due to thyroid hormone excess (Fell *et al.*, 1973).

Increased urinary zinc excretion has been observed in acromegaly, in which bone turnover may also be increased (Riggs *et al.*, 1972). Normally, a large percentage of the plasma zinc is bound to albumin. The albumin-bound zinc is in equilibrium with a small amino acid-bound fraction, and the latter is thought to be the major source of the zinc excreted in urine (Hambidge, 1977; Barness, 1978). The alteration in equilibrium with amino acid-bound zinc due to the increased tissue breakdown may be another cause of hyperzincuria in thyrotoxic patients. Freely exchangeable zinc is complexed with micro-molecular ligands, mainly the amino acids histidine and cysteine, and excreted via the kidney, but is

present in the small fraction in plasma (Giroux and Henkin, 1972). Therefore, the filtered load of zinc cannot be calculated simply on the basis of the total plasma zinc concentration as observed in hyperparathyroidism (Malette and Henkin, 1976). However, serum calcium and phosphorus were not measured in this study. The increased urinary zinc excretion in the presence of normal plasma zinc concentration does not necessarily indicate that increased renal clearance contributed to its increased excretion in hyperthyroidism.

The measurements of zinc concentration in erythrocytes may also be a useful parameter for assessment of the status of this mineral, since the turnover rate of zinc in these cells is slow. Lower zinc content in erythrocytes may suggest chronic, mild zinc deficiency in thyroid disease. The causes of abnormal zinc metabolism in thyroid disease are far from fully explained. Further studies are needed to establish the clinical significance of this abnormality and the role of zinc supplementation in thyroid disease.

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