Postgraduate Medical Journal (March 1977) **53**, 143–145.

Zinc metabolism and thyroid status

W. F. BREMNER
B.Sc., M.R.C.P.

G. S. FELL
Ph.D., M.R.C.Path.

University Departments of Medical Cardiology and Pathological Biochemistry, Glasgow

Summary

Urinary zinc excretion was found to be increased in patients with thyrotoxicosis when compared to euthyroid individuals. This increase did not appear to be due to an increase in creatinine clearance and was found to be strongly correlated with an index designed to assess the severity and acuteness of the metabolic response of the body to hyperthyroidism. The potential clinical significance of this finding is discussed.

Introduction

Plasma zinc levels and 24-hr urinary zinc outputs were measured in twenty-four thyrotoxic and ten hypothyroid patients. The findings were related to thyroid status, hormonal parameters, weight changes and to a scale assessing acuteness and severity of the metabolic response to hyper- or hypothyroidism.

Patients and methods

Thirty-four patients with unequivocal clinical evidence and biochemical confirmation of hyper- or hypothyroidism were studied. Hyperthyroid patients were selected on the basis of fairly severe symptomatology, particularly of rapid weight-loss.

Patients were scored on the Wayne Index (Crooks, Murray and Wayne, 1959; Billewicz *et al.*, 1969) as a first approximation of the clinical severity of thyroid malfunction. They were also assessed on a scale designed to give a measure of acuteness and severity of the metabolic response to thyroid over- or underactivity (Table 1). This rating was composed of rate of weight change (amount of weight-gain or loss/duration of symptoms), basal (resting) heart rate, fasting plasma cholesterol, serum thyroxine level and serum triiodothyronine level.

Plasma levels of zinc and 24-hr urinary zinc excretion were measured by the method of Peaston (1973). This method measures total zinc.

Zinc clearances (ml/min) were calculated as rate of urinary excretion over 24 hr (ml/min) × urinary zinc concentration ÷ plasma zinc concentration.

Serum thyroxine levels were measured by the Thyopac 4 (Amersham) method and serum triiodothyronine (T_3) levels by a radio-immunoassay procedure utilizing rabbit anti-human T_3 antiserum obtained from the National Institutes of Health, Bethesda (Ratcliffe, Challano and Ratcliffe, 1974).

Serum cholesterol was measured on samples obtained after a 12-hr fast by the automated method of Annan and Isherwood (1969).

Twenty-two patients were studied as out-patients and twelve as in-patients. All the patients were female, except for four thyrotoxic males. Ten healthy subjects, six female and four male, clinically and biochemically euthyroid, served as controls. The mean age and ranges for hyper- hypo- and euthyroid control groups were similar. All subjects studied had normal renal function as judged by plasma urea levels and creatinine clearances performed at the time of the zinc clearance studies. None of the female subjects, patients or controls, was taking oestrogen preparations, or other medications, that might interfere with serum protein and zinc binding parameters.

Results

Table 2 lists relevant data for subjects grouped according to thyroid status. Zinc clearances, but not plasma zinc levels were significantly higher in thyrotoxic patients compared with euthyroid or hypothyroid subjects ($P<0{\cdot}001$). Despite expressing the zinc clearance as the ratio of zinc clearance to creatinine clearance this finding persists. The measured parameters of zinc metabolism do not differ significantly in euthyroid and hypothyroid groups.

Table 3 details the degree of correlation between zinc clearance and other measures of thyroid status in thyrotoxic patients. Rate of weight-loss shows the best correlation ($r=0{\cdot}92$). The Wayne Index score correlates rather poorly ($r=0{\cdot}61$) whereas there is a highly significant correlation ($r=0{\cdot}86$) between the score for the index of severity and acuteness of metabolic response shown in Table 1.

Correlations for hypothyroid patients are not significant. It proved impossible to assess accurately the duration of symptoms as onset was usually insidious and so rate of weight-gain could not be estimated with any accuracy.

Correspondence: Dr W. F. Bremner, Department of Medical Cardiology, Royal Infirmary, Glasgow G4 0SF.

TABLE 1. Rating scale to assess acuteness and severity of metabolic response to thyrotoxicosis

Parameter Heart rate	Score	Parameter Serum cholesterol (mmol/l)	Score	Parameter Serum thyroxine (mmol/l)	Score	Parameter Serum triiodothyronine (nmol/l)	Score	Parameter Rate of weight-loss (kg/week)	Score
70–80	0	<2·59	5	<154	0	2·2–2·5	0	<0·27	1
81–90	1	2·59–3·63	4	154–180	1	2·6–3·0	1	0·28–0·32	2
91–100	2	3·64–4·66	3	181–206	2	3·1–3·5	2	0·33–0·36	3
101–110	3	4·67–5·70	2	207–232	3	3·6–4·0	3	0·37–0·41	4
111–120	4	5·71–6·73	1	233–257	4	4·1–4·5	4	0·42–0·45	5
>121	5*	>6·74	0	>258	5	4·6–5·0	5	>0·46	6
						>5·0	6		

* Including two patients in atrial fibrillation.

TABLE 2. Significance of relevant parameters measured in groups studied

Thyroid status	Thyrotoxic			Euthyroid			Hypothyroid	
	Mean	s.d.	P*	Mean	s.d.	P*	Mean	s.d.
No of patients	24			10			10	
Heart rate	100	12	<0·001	70	8	n.s.	65	15
Fasting serum cholesterol (mmol/l)	5·44	1·04	<0·05	6·22	0·78	<0·005	7·51	0·91
Serum thyroxine (nmol/1)	194	23	<0·001	105·5	17	<0·001	27	13
Serum tri-iodothyronine (nmol/l)	3·0	1·2	<0·01	1·7	0·2	<0·001	0·58	0·21
Plasma zinc (μmol/1)	14·74	2.23	n.s.	14·24	2·50	n.s.	14·12	2·39
Zinc clearance (ml/min)	0·70	0·33	<0·001	0·34	0·12	n.s.	0·32	0·05
$\frac{\text{Zinc clearance}}{\text{Creatinine clearance}} \times 100$	0·636	0·310	<0·001	0·309	0·110	n.s.	0.32	0·041

* P values calculated by paired t-testing.

TABLE 3. Correlations between zinc clearance and relevant parameters in twenty-four thyrotoxic patients

Parameter	Correlation coefficient
Heart rate (resting)	0·87
Rate of weight-loss	0·92
Serum thyroxine	0·71
Serum triiodothyronine	0·64
Serum cholesterol	0·60
Wayne Index	0·61
Severity/acuteness score	0·86
Plasma zinc	0·42

Discussion

It is perhaps surprising that despite widespread interest in zincuria, as an indicator of catabolism (Henry and Elmes, 1975), few studies have been performed in thyrotoxic patients who would seem to offer a good model for tissue catabolism. One study did report a fall in red cell zinc concentrations in thyrotoxics and considered this a possible specific action of thyroxine on red cell zinc metalloenzymes (Pengaro *et al.*, 1974).

This present investigation has demonstrated a significantly higher zinc output in urine in thyrotoxic patients compared to euthyroid or hypothyroid patients. The increase in zinc clearance in thyrotoxic patients is greater than may be explained by any increase in the creatinine clearance in thyrotoxic patients or by a decrease in euthyroid and hypothyroid patients. The ratio zinc clearance : creatinine clearance is still significantly different in thyrotoxic patients. This would tend to suggest that the increased zinc excretion is not a renal phenomenon but may reflect an increased extracellular fluid zinc loss.

The correlation between clearance and Wayne Index score was poor, possibly because the Index contains items (e.g. ocular signs) that relate more to the underlying pathogenesis of the disorder than to the severity of the metabolic changes induced by elevated hormone levels. The best correlation was with rate of weight-loss and a highly significant correlation with the rating devised to estimate the acuteness and severity of the body's metabolic response to thyrotoxicosis.

No significant correlations were found in the ten hypothyroid patients although five of them had marked weight-gain (> 12·5 kg). The onset of the disorder was insidious and the duration of the disorder uncertain, and this may explain the lack of positive findings. It may be that a study of zinc metabolism in 'acutely' hypothyroid patients would show evidence of zinc retention.

Plasma zinc levels were maintained in thyrotoxic patients (no significant difference from levels in euthyroid controls) despite the increased urinary losses.

The data presented here suggest that urinary zinc losses in thyrotoxicosis are correlated with catabolic status and not a specific effect of thyroid hormones on, say, zinc metalloenyzmes.

It has been suggested that tissue catabolism releases amino acids and other constituents into the circulation; these compounds form stable co-ordination compounds with zinc. Normally, some 10% of total plasma zinc exists in this form in equilibrium with a further 60–70% of plasma zinc loosely attached to plasma albumin. The remaining plasma zinc is largely present in chemical combination as part of the metalloprotein α_2 macroglobulin (Giroux and Hankin, 1972; Fell, 1975). The main excretory pathway for zinc is via the gut. Renal losses are in the form of low molecular weight complexes as these alone normally pass the glomerulus. The excessive losses described in severe thyrotoxicosis in this study indicate an increased loss of tissue breakdown products or an alteration in the equilibrium with albumin-bound zinc. It would be of interest to study further the plasma zinc fractions in thyroid disease to clarify this point and to evaluate further the significance of zincuria in thyrotoxicosis.

No clinically significant consequence of increased zincuria was noted in the thyrotoxic patients, but it seems likely that the occurrence of thyrotoxicosis in patients with malabsorption of zinc, phenylketonuria, prolonged parenteral nutrition, or other conditions where zinc is deficient (Fell, 1975; Halsted, Smith and Irvine, 1974) will exacerbate the latter disorders.

References

ANNAN, W. & ISHERWOOD, D.M. (1969) An automated method for the direct determination of total serum cholesterol. *Medical Laboratory Technology*, **26**, 202.

BILLEWICZ, W.Z., CHAPMAN, R.S., CROOKS, J., DAY, M.E., GOSSAGE, J., WAYNE, E.J. & YOUNG, J.J. (1969) Statsitical methods applied to the diagnosis of hypothyroidism. *Quarterly Journal of Medicine*, **38**, 255.

CROOKS, J., MURRAY, I.P.C. & WAYNE, E.J. (1959) Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Quarterly Journal of Medicine*, **38**, 211.

FELL, G.S. (1972) Zinc in clinical nutrition. *Scottish Medical Journal*, **20**, 101.

GIROUX, E.L. & HANKIN, R.I. (1972) Determination of zinc distribution between albumin and alpha-2 macroglobulin in human serum. *Biochimica et biophysica acta*, **273**, 64.

HALSTED, J.A., SMITH, J.C. & IRVINE, M.J. (1974) A conspectus of research on zinc requirements of man. *Journal of Nutrition*, **104**, 345.

HENRY, R.W. & ELMES, M.E. (1975) Plasma zinc in acute starvation. *British Medical Journal*, **4**, 625.

PEASTON, R.F. (1973) Determination of copper and zinc in plasma and urine by atomic absorption spectrophotometry. *Medical Laboratory Technology*, **30**, 249.

PENGARO, J.A., WEINSTEIN, M., DEVETAK, M.C. & SOTO, R.J. (1974) Red cell zinc and red cell zinc metalloenzymes in hyperthyroidism. *Acta endocrinologica*, **76**, 645.

RATCLIFFE, W.A., CHALLANO, G.S. & RATCLIFFE, J.G. (1974) A critical evaluation of separation methods in radioimmunoassays for total triiodothyronine and thyroxine in unextracted human serum. *Annals of Clinical Biochemistry*, **11**, 224.