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Thyroid Hormones in Insulin Requiring Diabetes before and after Treatment

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Summary. Thyroid hormones have been measured in normal subjects and insulin-requiring diabetic patients before and after treatment. Plasma thyroxine (T4) and 3, 3', 5-triiodothyronine (T3) concentrations were both low in diabetics, with T3 frequently in the hypothyroid range, while 3, 3', 5'-triiodothyronine (rT3) concentrations were elevated. All three returned to normal following treatment. T3 concentration was directly related to glucose utilization and metabolic clearance rate; and inversely related to plasma ketone body concentration. Thyroid hormone abnormalities in diabetes may reflect the degree of insulin-secreting capacity.

Key words: Thyroxine, triiodothyronine, reverse T3, glucose utilization, glucose metabolic clearance rate, ketones, oxygen consumption, cortisol, insulin.

Clinically euthyroid patients suffering from a variety of non-thyroidal illnesses have been shown to have low circulating concentrations of 3, 3', 5-triiodothyronine (T3), low normal concentrations of thyroxine (T4), high concentrations of 3, 3', 5'-triiodothyronine (rT3) and normal concentrations of thyrotrophin (TSH) [1]. Decreased circulating concentrations of T3 do not necessarily reflect decreased concentrations at the receptor site and the effect of plasma changes on metabolic rate has not been examined. We report here the presence of thyroid hormone abnormalities in untreated insulin-requiring diabetes and their relationships to abnormalities of fuel metabolism and to oxygen consumption.

Methods

Eleven male diabetic patients were studied. All were judged to require insulin on clinical grounds and none had received previous insulin therapy. Details are shown in Table 1. Seven patients presented with juvenile-type acute ketotic diabetes, (nos. 1–7), three with secondary failure after initial treatment with diet and oral hypoglycaemic agents (nos. 8–10) and one with diabetic retinopathy (no. 11), who was judged clinically to require insulin therapy. Oral hypoglycaemic agents were discontinued in patients with secondary failure at least 48 hours before the study. No other medication was taken and no other diseases were present. Ten patients were re-studied after at least one week's treatment with Actrapid and/or Rapitard insulin (Novo Industri, Copenhagen).

Thirteen healthy normal subjects were also studied, (7 males, 6 females). Mean age of the normal subjects was 38 years (range 21–60) and mean body weight 105% of ideal (range 90–132). Seven were studied on a second occasion to assess whether significant variation occurred between studies.

Informed written consent was obtained from all subjects. Insulin was withheld from treated diabetics on the morning of the second test. After an overnight fast, cannulation of an antecubital vein and a 30 minute rest period, blood was taken for hormone and ketone body estimations. Serum T3, T4, rT3 [2] and TSH [3] were measured by specific radioimmunoassay. The source of the three thyroid hormone antisera was sheep. Sensitivity of the T3, T4 and rT3 assays was 0.05 nmol l^{-1}, 3 nmol l^{-1} and 0.02 nmol l^{-1} respectively. Cross reactivity of T3 in the T4 assay was $< 0.5\%$ and of T4 in the T3 assay $< 0.1\%$. Cross reactivity of rT3 with T4 was $< 0.08\%$ and was corrected for. The detection limit of the

Table 1. Diabetic patients

Patient	Sex	Age	% Ideal body weight before and after insulin		Time between study (Days)
1	M	34	97	98	11
2	M	16	77	90	20
3	M	21	72	96	54
4	M	63	106	Died before 2nd study	–
5	M	29	79	81	9
6	M	41	84	96	41
7	M	27	89	92	11
8	M	33	79	87	14
9	M	53	89	90	10
10	M	63	95	99	99
11	M	51	101	108	18
Mean		39	88	94	29
SEM		5	3	2	9

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Table 2. Thyroid hormone measurements in diabetic and normal subjects

Diabetic patients	T4 nmol 1^{-1}		T3 nmol 1^{-1}		T4:T3 ratio		rT3 nmol 1^{-1}	
	(i)	(ii)	(i)	(ii)	(i)	(ii)	(i)	(ii)
1	88	84	0.88	1.51	100	56	0.48	0.09
2	52	90	0.64	2.63	81	34	1.43	0.22
3	39	59	0.18	1.44	216	41	0.82	0.26
4	62	–	0.58	–	107	–	0.83	–
5	103	105	1.12	1.40	92	75	0.25	0.18
6	65	83	0.80	1.60	81	52	0.22	0.15
7	45	62	0.40	1.70	113	36	0.28	0.09
8	70	67	1.01	1.25	69	54	0.49	0.29
9	82	90	1.40	1.90	59	47	0.48	0.47
10	88	96	1.80	2.40	49	40	0.08	0.22
11	77	70	0.71	1.32	108	53	0.46	0.18
Mean ± SEM	70±6	81±5	0.87±0.14	1.72±0.15	98±13	49±4	0.53±0.11	0.22±0.04
Normal subjects								
Mean ± SEM	88±5	82±10	1.64±0.08	1.61±0.13	54±2	52±6	0.17±0.04	0.17±0.06

Table 3. Glucose R_{ut}, MCR and plasma ketone body concentrations in diabetic patients before treatment

Patient	Glucose R_{ut}+ μmol min^{-1} kg^{-1}	Glucose MCR mls min^{-1} kg^{-1}	3-Hydroxybutyrate mmol 1^{-1}	Acetoacetate mmol 1^{-1}
1	*	*	1.600	0.716
2	5.4	0.464	2.050	0.816
3	7.0	0.493	5.370	1.274
4	7.8	0.438	6.620	1.639
5	15.7	1.083	1.019	0.439
6	9.6	0.683	6.380	1.257
7	7.9	0.718	1.897	0.694
8	15.6	0.987	0.294	0.159
9	19.1	1.329	0.281	0.154
10	11.9	1.116	0.257	0.155
11	13.4	0.725	0.362	0.187

* Urinary glucose loss was not measured in this patient
\+ glucose utilisation rate

TSH assay was 2 mU 1^{-1}, and the normal range up to 7.2 mU 1^{-1}. Thyroid hormones before and after treatment and from the two studies in normal subjects were measured in the same assay. Ketone bodies were measured enzymatically [4] and represent the sum of acetoacetate and 3-hydroxybutyrate. Glucose production rate (Ra) in the steady state was then estimated by injection of a bolus of 50 μCi of ^{3}H-3-glucose into a contralateral vein as validated by Hetenyi [5]. Glucose utilization rate (R_{ut}) was calculated by subtracting the urinary glucose loss during the test period from the isotopically measured Ra. Glucose metabolic clearance rate (MCR) could then be calculated by relating this to the plasma glucose concentration. Seven five minute collections of expired air into Douglas bags were made and the last five of these used to measure oxygen consumption [6].

Statistical significance was determined by Student's 't' test and linear regression by the least squares method [7]. Results from untreated diabetics were results from study in normal subjects.

Results

Plasma T4, T3, rT3 concentrations and T4:T3 ratios are shown in Table 2. Mean plasma T4 was 70 nmol/l ± 6 SEM in untreated diabetics and lower ($p<0.05$) than in normals (88 ± 5). Following insulin treatment, mean T4 rose to 81 ± 5 : although the rise was not significant, values were not significantly different from normal. Pre-treatment T3 concentrations were also lower ($p<0.001$) than normal (0.87 nmol/l ± 0.14 compared to 1.64 ± 0.08) and rose after insulin treatment to 1.72 ± 0.15 ($p<0.001$). The depression of T3 concentrations was more marked than that of T4 in the untreated diabetic and this was reflected in a significantly ($p<0.01$) higher T4:T3 ratio (98 ± 13 compared to 54 ± 2 in normals).

Mean rT3 concentration was higher ($p<0.01$) in untreated diabetics than control subjects (0.53 nmol/l ± 0.11 compared to 0.17 ± 0.04) and fell ($p<0.05$) on insulin treatment to 0.22 ± 0.04.

The T3:rT3 ratio was lower ($p<0.01$) in untreated diabetics (3.80 ± 1.91 compared to 15.11 ± 2.69 in normals).

TSH remained suppressed in both groups of patients, detectable concentrations only being found in two ketotic diabetics (patients 3 and 7 : 3.3 and 2.4 mU 1^{-1} respectively) whose T4 concentrations were in the hypothyroid range. T4 rose and TSH was undetectable in these two patients after insulin therapy. T3 was directly related to glucose R_{ut} ($r = 0.67$, $p<0.05$), to glucose metabolic clearance rate (MCR) ($r = 0.84$, $p<0.01$) and inversely to plasma ketone body concentrations ($r = -0.60$, $p<0.05$) in the untreated diabetics. Oxygen consumption was higher in ketotic diabetics and correlated with plasma ketone body concentrations ($r = 0.79$, $p<0.01$); it was higher in patients with lower T4 concentrations ($r = -0.64$, $p<0.05$) and lower T3 concentrations ($r = -0.56$, $p<0.10$). A significant inverse correlation was found between rT3 and glucose MCR ($r = -0.63$, $p<0.05$), but not with glucose R_{ut} ($r = -0.52$). Results of glucose R_{ut}, MCR and plasma ketone bodies in diabetic patients before treatment are shown in Table 3.

No significant differences were observed in normal subjects studied on two occasions. Full details of results in normal subjects will be reported elsewhere [8].

Discussion

The changes in circulating thyroid hormone concentrations in our untreated diabetic patients clearly resemble those seen in other acute and chronic illnesses. Measurements of plasma T3 and T4 are therefore not reliable indicators of thyroid status in the untreated insulin-requiring diabetic. Similar findings have also been reported in patients with severe uncontrolled diabetes, whom it may be presumed also required insulin treatment [9]. Although a transiently and slightly increased secretion of TSH was found in a study of thyroid hormones in myocardial infarction [10], detectable TSH concentrations were only found in two of our patients whose T4 concentrations were below the normal range (defined as ± 2 S. D.). Even in these two subjects the increase in TSH was slight. Thyroidal status is more closely linked to the concentration of free rather than total plasma hormones and other workers have observed that, in contrast to free T3, free T4 may be normal [11] or even elevated [12] in other nonthyroidal diseases. A normal free T4 index was found in the study by Liewendahl and Helenius [9] and it is therefore possible that the low T4 in our study reflects a decrease in plasma thyroid hormone binding proteins. The relationship between T4 and glucose MCR and R_{ut} could then indicate a correlation between the degree of insulin lack and thyroid hormone binding proteins. However, as rT3 is inversely related to glucose MCR and R_{ut}, it seems unlikely that changes in T3 could result purely from changes in binding proteins.

The main source of circulating T3 and rT3 is believed to be the peripheral deiodination of T4, rather than thyroidal secretion [1]. The divergent changes in T3 and rT3 suggest that the fall in T3 is due to preferential monodeiodination of T4 to rT3 in the periphery, rather than, or as well as, an overall decrease in iodination. As Westgren has pointed out [10], divergent changes in T3 and rT3 could hardly result from altered thyroidal secretion of iodothyronine as TSH produces parallel, not divergent changes in T4, T3 and rT3.

Among our diabetic patients there was a range from the non-ketotic patients with "secondary failure" to the acute ketotic diabetic. The inverse relationship between T3 and plasma ketones shows that changes in thyroid hormone metabolism are related to the degree of ketosis. Similarly, the correlation between T3 and glucose R_{ut} and MCR shows that the failure to maintain normal glucose metabolism is also associated with increasing severity of the thyroid hormone abnormalities. As ketosis and depressed glucose R_{ut} may indicate the degree of insulin lack, plasma T3 may be an index of residual insulin secreting capacity in the untreated insulin requiring diabetic. However, since similar thyroid hormone changes have been found in Cushing's disease [1] in which fasting ketones and glucose R_{ut} are normal (unpublished data), a direct causal relationship between T3, plasma ketones and glucose R_{ut} seems less likely than an indirect one. A role has been proposed for glucocorticoids as they depress T3 and increase rT3 when given to healthy volunteers [13]. In addition, administration of maintenance doses of hydrocortisone to patients with primary adrenal insufficiency and pharmacological doses to euthyroid subjects causes suppression of both thyroidal iodine release and TSH [14]. In our patients, cortisol was initially elevated and fell after insulin treatment, but no correlation was seen between plasma cortisol and thyroid hormone concentrations.

It has been speculated that the purpose of the fall in T3 and rise in rT3 concentrations in disease states is to protect the subject against the effects of increased tissue catabolism [15]. This is achieved by decreasing energy requirements in response to lowered T3 concentrations, rT3 simultaneously inhibiting the actions of T3 by occupying peripheral binding sites and interfering with feedback control by occupying pituitary binding sites. Although our data cannot refute such a hypothesis, the increase in oxy-

gen consumption with fall in T3 concentrations does show that such compensation can at best, only be partial.

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