The importance of reverse triiodothyronine in hypothyroid children on replacement treatment

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SUMMARY Reverse triiodothyronine (rT3), triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) values were measured by radioimmunoassay in 40 children with congenital hypothyroidism who were being given levothyroxine (0.05–0.35 mg/day) and in 14 normal controls. In 15 of the children with hypothyroidism the treatment, judged by serum T4 and TSH values and thyrotrophin releasing hormone (TRH) test, seemed to be adequate and their mean rT3 value and rT3:T4 ratio were comparable with the controls. The remaining 25 children had a raised serum T4 and a low TSH value. Only 4 (16%) of these children had an abnormally high T3 concentration but the rT3 value was raised in 23 (92%) and their mean rT3 value and rT3:T4 ratio were significantly higher than in the control children. Less than 20% of this 'overtreated' group, however, had clinical hyperthyroidism.

We suggest that in patients on T4 replacement treatment the peripheral thyroid homeostatic mechanisms produce larger amounts of rT3, thereby preventing high T3 values where serum T4 values are raised. This may explain why the 'overtreated' children showed no clinical evidence of hyperthyroidism. These findings emphasise the protective and selective role of peripheral monodeiodination.

In the past the adequacy of thyroid replacement treatment was judged by clinical and radiological criteria. We undertook to evaluate the efficacy of these criteria by estimating thyroid hormone and thyroid stimulating hormone (TSH) values; serum reverse triiodothyronine (rT3) was also estimated. This report forms part of a study on 66 hypothyroid children in which we showed that unusually large doses of levothyroxine (L-T4) were used.¹ In 40 patients rT3 values were available and we analyse the data and the probable importance of rT3 in children receiving replacement treatment.

Material and methods

Serum triiodothyronine (T3), thyroxine (T4), TSH, and rT3 were estimated in 40 children with congenital hypothyroidism who were receiving regular replacement treatment and in 14 normal controls. The children were aged between 1 and 14 years. Diagnosis had been established by the usual clinical and laboratory criteria. The hypothyroid children included here had received L-T4 in doses ranging from 0.1–0.35 mg/day over a period varying from 12 months–12 years. A body weight based dose schedule was not used. Periodic clinical evaluation,

anthropometric assessment, and bone age determination (Greulich and Pyle standard) were available for all children.

The serum T3 and T4 concentrations were estimated using kits prepared by BARC (Bhabha Atomic Research Centre), India. The minimal detectable value for T3 was 0.125 ng/ml and for T4 was 1.2 ng/ml. Quality control was maintained by using pooled serum dispensed in small vials and preserved at –20°C: one of these was assayed with every batch. The tests and standards were run in duplicate. The interassay percent coefficient of variation was 10.9 for T3 and 7.9 for T4. rT3 was estimated by radioimmunoassay (RIA) (code 1834 Hypolab A A Coinsins, Switzerland). The RIA kit contained a quality control test, and the sensitivity of the assay was 0.06 ng/ml. The TSH was estimated by RIA using the double antibody technique of Midgley. Reagents were kindly supplied by the National Institute of Health, Bethesda, USA. The sensitivity of the TSH assay system was 1 µU/ml. All determinations were carried out in duplicate. Results were expressed in µU of the 68/38 International human TSH standard.

The adequacy of treatment was judged by the values of serum T4, TSH, and the thyrotrophin

releasing hormone (TRH) test. The TSH response to 7 µg/kg of TRH was studied in 13 of the 40 hypothyroid children whose serum T4 ranged between 120 and 150 ng/ml (156 to 195 nmol/l) to differentiate between adequately treated and overtreated groups. The L-T4 doses were reduced, when necessary, to between 5 and 10 µg/kg, depending on age. The hormone estimations were repeated 6 weeks or more after reduced doses. Therapeutic compliance was always ascertained. The clinical and radiological criteria were correlated with the hormone values.

Results

The mean serum T3, T4, and rT3 values of the control children are shown in Table 1. The serum TSH values in all the controls were less than 10 µU/ml. Based on the serum values of T4, TSH, and TRH tests, 25 of the 40 hypothyroid children on replacement treatment could be classified as overtreated. Their T4 values exceeded 140 ng/ml (182 nmol/l) (Fig. 1) and the serum T4 value, mean (SD) 202.3 (64.1) ng/ml (262.7 (83.1) nmol/l) was significantly raised in comparison with controls and adequately treated children ($P < 0.01$) (Table 1). The TSH values were less than 1.65 µU/ml in 50% of this group and in the others the values were between 1.65 and 3 µU/ml. In 8 of these 25 children the serum T4 concentration was between 140 and 150 ng/ml (182 and 195 nmol/l) and the estimation of TSH, 30 minutes after intravenous TRH, showed no change from the basal TSH of 1.65–3 µU/ml. This lack of response favoured excessive treatment.

The T3 value in the overtreated group, mean SD 1.53 (0.76) ng/ml (2.34 (1.17) nmol/l) was not significantly different from the controls or adequately treated children ($P > 0.05$). In 4 of the overtreated children the serum T3 values exceeded the upper normal limit, with values ranging from 2.5–4 ng/ml (3.84–6.14 nmol/l) (Fig. 1).

The rT3 value, mean (SD) 0.737 (0.366) ng/ml (1.13 (0.56) nmol/l) in the overtreated group was significantly higher than in the control group and in children on adequate treatment ($P < 0.01$) (Table 1). The mean rT3:T4 ratio in the overtreated group was also significantly higher compared with controls and adequately treated children ($P < 0.01$).

Fifteen hypothyroid children who could be classified as adequately treated had serum T3 and T4 values of mean (SD) 1.19 (0.54) ng/ml (1.83 (0.83) nmol/l) and 108 (12.9) ng/ml (140.26 (16.75) nmol/l) respectively (Table 1). Their TSH values ranged from 3–8 µU/ml. In five of this group, in whom the serum T4 was between 120 and 130 ng/ml (156 and 169 nmol/l) after intravenous TRH, TSH rose from a basal value of 3–5 µU/ml to between 12 and 20 µU/ml at 30 minutes. This response confirmed that the L-T4 doses were adequate. The rT3 value of these 15 children was, mean (SD) 0.265 (0.078) ng/ml (0.41 (0.12) nmol/l) and the rT3:T4 ratio was, mean (SD) 0.0026 (0.0008); similar to the values obtaining in control children (Table 1).

In four of the children with raised serum T4 and rT3 values, the L-T4 doses were reduced and hormone estimations were repeated. The resultant reduction in the serum T4 values was accompanied

Table 1 Serum reverse triiodothyronine (rT3), triiodothyronine (T3), and thyroxine (T4) values and rT3:T4 ratios in children with hypothyroidism treated with levothyroxine and controls

Group	No	Values	rT3 (ng/ml)	T3 (ng/ml)	T4 (ng/ml)	rT3:T4
Control children*	14	Mean	0.214	1.27	122.9	0.0019
		SD	0.104	0.58	18.51	0.0011
		SE	0.028	0.16	4.95	0.0003
Adequately treated children with hypothyroidism	15	Mean	0.265	1.19	108.0	0.0026
		SD	0.078	0.54	12.9	0.0008
		SE	0.020	0.14	3.3	0.0002
Overtreated children with hypothyroidism	24†	Mean	0.737	1.53	202.3	0.0038
		SD	0.366	0.76	64.1	0.0014
		SE	0.073	0.15	13.1	0.0003

Conversion: traditional units to SI—rT3, 1 ng/ml = 1.536 nmol/l; T3, 1 ng/ml = 1.536 nmol/l; T4, 1 ng/ml = 1.3 nmol/l.

Overtreated v adequately treated children and overtreated v control children: rT3 = $P < 0.01$; T3 = $P > 0.05$; T4 = $P < 0.01$; rT3:T4 = $P < 0.01$. Adequately treated v control children: no difference in rT3, T3, T4 or rT3:T4 ($P > 0.05$).

Test used, Student's *t* test after initial application of F test.

*The normal and adequately treated hypothyroid children were not strictly age matched and inclusion of 4 infants (aged 1 year) may explain the slightly higher mean T4 in the control group.

†One of the 25 patients was not included in statistical calculation as exact numerical values were not available: his values were rT3 > 2 ng/ml, T4 > 200 ng/ml and T3 = 2.7 ng/ml.

Fig. 1 Serum triiodothyronine (T3), reverse triiodothyronine (rT3), and thyroxine (T4) values in adequately treated (A) and overtreated (B) children with hypothyroidism.

Conversion: traditional units to SI—rT3, 1 ng/ml=1.536 nmol/l; T3, 1 ng/ml=1.536 nmol/l; T4, 1 ng/ml=1.3 nmol/l.

by a simultaneous decline in rT3 concentrations (Fig. 2).

The lack of overt clinical hyperthyroidism among these 25 overtreated hypothyroid children with raised T4 concentrations was of interest. Fifty percent had no symptoms or signs. Table 2 shows the frequency of clinical manifestations suggestive of iatrogenic hyperthyroidism. Increased growth velocity, defined as a growth rate above the mean for the age, was observed in five patients. A lag of about

12–18 months in bone age among Indian children compared with values in the Atlas of Gruelich and Pyle, is known. Taking this into account, it was noted that only four of the overtreated group had a bone age corresponding to their chronological age and it was surprising that bone age did not exceed the chronological age in any. In the remaining children the deficit in bone age compared with chronological age, varied between 18 months and 3 years.

Four of the 25 overtreated children who had raised T3 and T4 concentrations were on high dose replacement treatment for more than two years. Their rT3 values varied from 0.6–2 ng/ml (0.92–3.07 nmol/l). Two of them had irritability, and one had a short attention span. Accelerated growth velocity was noted in one. Two had a bone age deficit of 12–24 months and in the other two, bone age corresponded with the chronological age.

Discussion

rT3 is a normal component of human serum and thyroglobulin.² Peripheral metabolism of T4 is the

Table 2 Symptoms and signs of hyperthyroidism in hypothyroid children receiving excessive T4 treatment (n=25)

Clinical manifestations	No	(%)
Asymptomatic	13	(52)
Increased appetite	—	—
Excessive sweating	—	—
Irritability	4	(16)
Diarrhoea	3	(12)
Tachycardia	4	(16)
Tremors	—	—
Weight loss/poor weight gain	3	(12)
Increased height velocity	5	(20)
Advanced bone age	—	—

Fig. 2 Serial fall in reverse triiodothyronine (rT3) values along with reduction in thyroxine (T4) and triiodothyronine (T3) concentrations with reduced levothyroxine (L-T4) dose.

Conversion: traditional units to SI—rT3, 1 ng/ml = 1.536 nmol/l; T3, 1 ng/ml = 1.536 nmol/l; T4, 1 ng/ml = 1.3 nmol/l.

major source of rT3:^{3,4} about 97.5% of the serum rT3 is derived from T4 monodeiodination and only 2.5% is produced by the thyroid gland.⁵ rT3 is believed to have no biological activity and is calorigenically inactive.⁶ The formation of rT3 from T4 is regarded as an inactivating pathway of T4 metabolism. rT3 may play a part in the metabolic

regulation and biological action of T4.² The degradation of rT3 is three times more rapid than that of T4, hence the very low serum concentrations of rT3. Reciprocal alterations in serum rT3 and T3 concentrations such as an increase in rT3 and a reduction in T3 are reported in a number of non-thyroidal acute and chronic illnesses, starvation,

and in the newborn.⁸⁻¹⁰ A raised serum rT3 value is described in patients with endogenous T4 as well as T3 thyrotoxicosis.^{2,11}

In hypothyroid patients on thyroid replacement treatment the basic peripheral mechanisms for metabolic deiodination of T4 to T3 and rT3 are intact.^{2,7} This is shown by the simultaneous increase in both these fractions along with serum T4 when thyroxine treatment is begun. In a recent study in hypothyroid adults with progressive increments in the dosage of thyroxine, a simultaneous increase in serum T4, T3, rT3 and the rT3:T4 ratio was described.¹¹ Changes in the concentrations of serum T3 and rT3 were noted with starvation in patients whose thyroid function was suppressed by giving exogenous T4.¹²

Some important findings have come from our study. In the adequately treated group the serum values of T4, T3, rT3, and the rT3:T4 ratio were all within normal limits, but the mean serum rT3 value was considerably raised and the rT3:T4 ratio was appreciably higher in children receiving excessive doses of L-T4. The fact that serum T3 was not raised in most (21 of 25) overtreated patients, all of whom had very high serum T4 concentrations, was notable. The physiological mechanisms probably diverted larger amounts of T4 along the peripheral inactivating pathway to form larger amounts of rT3, and prevented a raised T3 value. This may act like a defence mechanism, protecting the tissues from excessive metabolic stimulation. This observation supports the integrity of the peripheral mechanisms of the major inactivating pathway of T4 metabolism in hypothyroid children on long term replacement treatment.

The absence of clinical manifestations of hyperthyroidism in most of the overtreated children was interesting. Fifty two percent had no clinical symptoms or signs and accelerated growth velocity was observed in only 20% of the group. The physiological pathway for T4 degradation and metabolism, besides being important in thyroid hormone homeostasis, probably plays a protective role and prevents a raised concentration of T3—a hormone which is four times as potent as T4 in its biological effects. It has recently been postulated that T4, although not devoid of calorogenic and biological effects, may behave more like a reservoir or prohormone for T3.¹³ This may partly explain the absence of clinical hyperthyroidism in patients with very high T4 values. The metabolic derivatives of rT3—diiodothyronines, and in particular 3, 5-diiodothyronine—are potent inhibitors of T4 to T3 conversion.¹⁴ rT3 itself can inhibit the calorogenic action of T4 and T3 in man.¹⁵ It has been

used to treat hyperthyroidism.¹⁶ It inhibits monodeiodination of T4 to T3, though it is not antagonistic to T4 in all its effects.¹⁷ Formation of rT3 may not be the only factor which determines the propensity to develop overt manifestations of T4 induced hyperthyroidism. Protein binding, the available concentrations of free hormones, and individual differences in the rate of thyroid hormone degradation and clearance may be other important factors that need further study.

A reciprocal relation often exists between T3 and rT3, but in our study the relation was analogous to endogenous T4 thyrotoxicosis where rT3, T4, and T3 are raised. We suggest that the activation of body homeostatic mechanisms that result in the production of larger amounts of rT3 protect most children with hypothyroidism from iatrogenically induced hyperthyroidism by shunting peripheral T4 metabolism from an activating to an inactivating pathway. As this study includes patients with little functioning thyroid tissue, it gives further credence to the postulation by Chopra *et al.* that peripheral monodeiodination of T4 is not a random process.² It is selective and is probably modified by the biological needs of the individual.

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