Hyperthyrotrophinaemia during thyroxine replacement therapy

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Summary: During the follow-up of 224 cases of treated hypothyroidism, 14 clinically euthyroid patients were found to have elevated serum thyrotrophin and normal total thyroxine concentrations. Closer observation of these patients during the following 27 months resulted in the serum thyrotrophin levels returning to normal spontaneously in 8 patients (Group 1) whilst remaining elevated in 6 (Group 2), despite no significant differences in thyroid hormone levels between the two groups. Serum thyrotrophin in Group 2 patients remained high until an additional 50 µg/day thyroxine was prescribed although only 2 patients noted any benefit. Non-compliance or inadequate dosage of thyroxine are the probable causes of this sub-clinical hypothyroidism. Thyroid hormone estimations fail to differentiate the two conditions and we recommend a period of closer observation before making any thyroxine dosage adjustments in order to detect non-compliance.

Introduction

The diagnosis of hypothyroidism is important since thyroxine therapy restores most patients to normal health. A large study of patients on replacement therapy indicated that this is a simple process for the majority, although the cumulative incidence of under treatment was 13.2% over a 10 year period.¹ To simplify and standardize thyroxine therapy, various dosage schedules have been promoted,^{2,3} and various strategies proposed to monitor this treatment.^{4,5} The plethora of publications on these subjects demonstrates that there are a few patients for whom assessment of thyroxine replacement is not so easy. On appraisal of more than 200 patients receiving replacement therapy we discovered 14 such 'problem' patients and report here our investigations and conclusions.

Patients and methods

Between 1 January 1983 and 31 December 1983, 224 patients receiving thyroxine replacement therapy were reviewed in the thyroid clinic. Fourteen of these patients (11 women and 3 men) were noted to have elevated serum thyrotrophin (TSH) despite being assessed clinically as being euthyroid and having normal serum total thyroxine. These patients had been

commenced on thyroxine replacement therapy 8 months to 12 years (median 2 years) earlier with an initial fall in serum TSH to normal values in all cases. No recent dosage changes were noted and all patients stated that they were taking their medication routinely and were thought to be reliable. These patients were followed up at 3–6 month intervals in the thyroid clinic over a period of 27–30 months.

Blood was taken at the start of the study and after 27 months during single sittings at least 4 hours after their daily thyroxine dosage (100–200 µg). Those patients with persistently elevated serum TSH at 27 months were given an additional 50 µg of thyroxine and a further blood sample taken 3 months later.

Radioimmunoassay methods were used for the measurement of: total thyroxine (T4): In-house, double antibody-polyethylene glycol (PEG) precipitation. Free thyroxine (FT4) and free tri-iodothyronine (FT3): Amersham International, analogue method. TSH: In-house, double antibody – PEG precipitation. Thyroxine binding globulin (TBG): CIS (UK) Ltd, double antibody. Reverse triiodothyronine (rT3): Sero diagnostics, double antibody PEG-precipitation. Reference ranges for the assays are given in Table I.

Results between groups were compared statistically using the Mann-Whitney U-test.

Results

The results are summarised in Table I.

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Table 1 Thyroid function test results for the 14 treated hypothyroid patients. Results expressed as means and ranges

	Month	Total T4 (60–160 nmol/l)*	FT4 (9.0–25.0 pmol/l)*	FT3 (3.7–9.2 pmol/l)*	TSH (< 5 mU/l)*
Group 1 (n = 8)	0	105 (80–130)	16.9 (11.5–26.1)	5.1 (4.0–6.7)	20.9 (14.1–32.8)
	27	130 (68–163)	16.8 (7.9–24.7)	5.4 (4.2–9.5)	– (<1.9–3.2)
Mean age 48 years (17–70)		117 (82–146)	14.9 (8.2–19.9)	3.9 (2.7–4.5)	22.6 (12.0–34.9)
Group 2 (n = 6)	0	111 (100–139)	14.0 (10.1–17.0)	4.3 (3.6–5.3)	15.5 (9.2–21.8)
	27				
Mean age 55 years (28–66)	30	128 (108–150)	20.9 (14.3–28.8)	4.8 (4.3–5.4)	– (<1.9–4.9)

* Reference range.

Initially normal concentrations of total T4 and elevated concentrations of TSH were observed in all patients. Five patients had low free T3 and two patients had low free T4 concentrations. During 27 months of follow-up it was apparent that the 14 patients fell into two groups. Group 1 (6 females and 2 males) in which TSH returned spontaneously to normal and Group 2 (5 females and one male) with persistently elevated TSH. No significant differences in free thyroid hormone levels were noted between the two groups although total T4 in Group 1 patients increased significantly ($P < 0.05$) over the observation period. Addition of 50 µg/day thyroxine to the daily dosage of Group 2 patients normalized TSH over a period of 3 months in all patients with a significant ($P < 0.05$) increase in free T4. No significant changes in total thyroxine or FT3 were observed. All patients had normal concentrations of TBG and reverse T3.

Discussion

Monitoring of patients receiving thyroxine replacement therapy is important since undertreatment may be a predisposing factor in coronary artery disease⁶ and patients with cardiac disease may be unable to tolerate even a normal thyroxine dosage.⁷ Differentiation between patients on suboptimal thyroxine replacement and those failing to comply was not

possible by clinical or biochemical assessment, at the commencement of our study. An increase in subsequent follow-up clinic visits demonstrated a number (8) of patients in whom the TSH returned spontaneously to normal. These patients were presumed to be non-compliant and were now taking their treatment regularly, in response to more frequent hospital attendance. The other 6 appeared to be receiving sub-optimal therapy and responded to an additional 50 µg/day of thyroxine. These 6 patients were reliable and no changes in thyroxine dosage prior to the study period were noted to explain the rise in TSH. The Scottish Automated Follow-up Register Group found undertreatment to be a common problem in thyroxine replacement. The use of serum thyroxine as a screening test may have caused them to underestimate the problem. Using their approach we would have missed 9 of the 14 patients in this study. TSH is the most sensitive indicator of undertreatment and where thyroid status is in doubt we recommend, in addition to its measurement, more frequent clinic visits.

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