Lacking evidence for release of thyroid hormones from circulating thyroglobulin during subtotal thyroidectomy

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Abstract. The effect of subtotal thyroid resection for thyrotoxicosis on concentrations of serum thyroid hormones and thyroglobulin (Tg), was determined in 10 patients during operation and the subsequent 18 days. Mean serum Tg responded drastically, increasing from a pre-operative value of 0.30 nmol/l to a peak value of approximately 26 nmol/l during operation followed by a gradual decline to levels lower than before surgery on day 18. Mean serum total thyroxine was 114 nmol/l pre-operatively and free thyroxine index (FT4I) 105 units. Both fluctuated only slightly during operation. Postsurgically, the mean values decreased to below 50% of the pre-operative level. Mean serum total triiodothyronine (T3) was 1.46 nmol/l pre-operatively. It decreased during operation, reaching a nadir of 0.55 nmol/l on day 2, whereafter the concentration increased slightly. Mean serum reverse T3 (rT3) was 0.45 nmol/l pre-operatively, increased 62% during surgery, and decreased postsurgically. The mean value of serum thyroid stimulating hormone (TSH) was 0.61 mU/l pre-operatively and remained below 1 mU/l during and after operation, but from day 10 concentration began to rise steadily. It is concluded that the vast release of Tg during thyroid resection did not contribute to the concentration of serum T4 to an extent of clinical relevance.

In previous studies it has been shown that thyroid resection for thyrotoxicosis leads to a drastic increase in circulating levels of thyroglobulin (Tg) (Bech et al. 1982). In vivo studies in rats have demonstrated that thyroid hormone is released into the circulation from injected Tg (Taura et al. 1986). Whether or not the excessive amount of Tg released into the blood stream during thyroid surgery in thyrotoxicosis influences the level of thyroid hormones in serum to an extent of clinical importance remains to be clarified. The question rises since thyroid crisis following thyroid resection for thyrotoxicosis appears immediately after surgery with an average interval being approximately 8 h (Ransom & Bayley 1934; Thompson & Fry 1964). Although the pathogenesis of thyroid crisis is poorly understood, one underlying mechanism may be attributed to excess thyroid hormone secretion (Hedge 1969) or disturbances in thyroxine binding (Brooks & Waldstein 1980).

The purpose of the present investigation was to study the acute changes in serum thyroid hormones following subtotal thyroid resection for thyrotoxicosis with a special reference to their relation to serum Tg alterations.

Patients and Methods

Patients and sampling
The series comprised 10 thyroglobulin-antibody negative patients, 9 females and 1 male, mean age 48 years, range 26 to 64 years. All patients were subjected to subtotal resection of the thyroid gland for thyrotoxicosis. Eight goitres were nodular and 2 diffuse. Pre-operatively, hyperthyroidism was treated with thiamine...
zole for 1–10 years, median 2 years, in all patients, supplemented with 1-thyroxine in 7 patients. The remaining 3 were given iodine the last 10 days before surgery. In only one patient the medical treatment was given for 10 years. She was young at the time of diagnosis, had a goitre of small size, but experienced relapse several times after cessation of antithyroid drug. The operation was standardized and performed by the same surgeon. The amount of thyroid tissue left was approximately 4–6 g. At an average the removed tissue weighed 118 g, range 48–224 g.

Prior to operation, a control sample of blood was collected. This sample and the following samples were collected with patients in supine position from a peripheral vein. Systematically, samples were drawn at induction of general anesthesia, at removal of each thyroid lobe, respectively, and at 1, 2, 4, 8 and 24 h after tissue resection. On the following 4 days blood samples were taken daily, then on the 10th and 18th day at 08.00 h. General anesthesia was induced iv with a mixture of dehydrobenzperidol, fentanyl and pancuronium bromide supplemented with thiopental. Post-operatively, the antithyroid drugs including 1-thyroxine were withdrawn.

Assay

Serum Tg was measured by a 'sandwich type' immunoradiometric method (CIS, Sorin). The detection limit was approximately 0.007 nmol/l and the reference interval of 100 healthy controls was < 0.135 nmol/l. The total imprecision was 6–15% (cv) and the within series cv 7–8% in the concentration range 0.035–15 nmol/l. Serum TgAb was measured by a radiocorpilation method (Date et al. 1980) using Medical Research Council Standard A 93/65 (reconstituted content per definition 1000 kU/l). The detection limit was 2 kU/l. The total imprecision in the concentration range studied was 8–12% (cv) and within series imprecision 3–4%.

Serum total thyroxine (TT4) was measured by Gamma Coat® from Clinical Assays, Travenon-Genentech Diagnostics (Cambridge, MA). The 95% reference interval was 65–135 nmol/l and the imprecision 6% and 5% (cv, total and between series, respectively). Likewise, the triiodothyronine uptake test (T3U) was measured by Gamma Coat®. The 95% reference interval was 0.82–1.12 arbitrary units. Total and between series imprecision cv 4%. Serum total triiodothyronine (TT3) was measured by Amerlex® T3 RIA kit (Amersham

![Graph](image-url)

**Fig. 1.**

Serum concentrations of thyroglobulin (mean ± SEM). Levels of statistical significance given by ▲ (5% level) or ▲▲ (1% level) (Wilcoxon paried test). AN = during anesthesia before skin incison; L1 and L2 = resection of first and second thyroid lobe.
International, UK) with a 95% reference interval: 1.0–2.1 nmol/l and an imprecision of 5 and 3%, respectively (CV total and within series).

Serum thyroid stimulating hormone (TSH) was quantified by a double-antibody liquid-phase radioimmunoassay NHS-TSH®, Diagnostic Products, USA. The 95% reference interval was <3.8 mU/l. The lower detection limit was 0.5 mU/l and the imprecision 2% (CV total and between series). Serum reverse T3 (rT3) was determined using the PEG RIA kit of Serono Diagnostics (Braintree, MA). The 95% reference interval was 0.23–0.54 nmol/l. Total imprecision was 13% (CV); within series 9%. FT4I was calculated by multiplication of serum TT4 concentrations with T3U (arbitrary units).

Statistical methods
The Wilcoxon paired, signed-rank test was used for significance testing.

Results

Mean serum Tg concentration was elevated preoperatively, 0.30 nmol/l, extremes 0.09–0.55 nmol/l (Fig. 1). Tg values increased rapidly during resection of thyroid lobes, peaking after the second lobe, mean 26 nmol/l with large individual differences (0.7–88 nmol/l). Afterwards Tg declined gradually reaching nadir values on day 18, mean 0.16 nmol/l.

Pre-operative mean FT4I (Fig. 2), calculated by the formula $TT_4 \times T3U$, was 105 arbU, extremes 41–158. A transient decline was registered initially followed by a small peak at the time of resection of the second lobe, albeit not significant. Subsequently, a gradual descent appeared reaching a nadir level of 44 arbU on day 18. Serum TT4 values varied before surgery between 55–174 nmol/l, mean 114 nmol/l. Initially during surgery the level showed a transient decrease. Postoperatively, the mean TT4 concentration fell steadily to 53 nmol/l on day 18. Mean T3U was 0.92 arbU before operation, extremes 0.74–1.23. During induction of anesthesia and the following 4 h, the level ascended significantly, peak 1.03 arbU. The curve then presented a fall until day 5, whereafter values flattened out at a significantly lowered level, mean 0.77 on day 18, compared with control value.

Serum TSH values (Fig. 2) were low pre-operatively in all patients, mean 0.61 mU/l. Only neg-

![Fig. 2.](https://www.bioscientifica.com/ppc/servlet/doi/10.1046/j.1365-2141.1999.00058.x)

Serum concentrations of TSH (U/l) and free T4-index (arbitrary units, mean ± SEM). (Signs and abbreviations as for Fig. 1).
ligible changes were noticed until day 10, when a steady rise began reaching a mean value of 4.6 mU/l on day 18, extremes 0.9–15.5 mU/l.

Mean serum TT₃ (Fig. 3) decreased from a pre-operative value of 1.46 nmol/l, extremes 0.79–1.97 nmol/l, to 1.15 nmol/l at the time of first lobe resection. After surgery the decline continued rapidly until day 2, mean 0.55 nmol/l, whereafter the level stabilized at approximately 0.6 nmol/l.

Conversely, rT₃ ascended from 0.45 nmol/l, (extremes 0.25–1.02 nmol/l) to 0.73 nmol/l on the first postoperative day. Then a rapid fall took place followed by a more gradual decline (Fig. 3).

Discussion

To our knowledge, measurements of peripheral thyroid hormones in relation to surgery upon the thyroid gland are remarkably sparse. Generally, only changes during follow-up examinations have been reported, whereas results achieved during the operation or immediately postoperatively have not been included. Matte et al. (1981) described a pronounced fall in serum TT₃ values on day 2 after hemithyroidectomy in 8 patients with a solitary cold nodule without significant alterations in TT₄. Feely et al. (1981) demonstrated unchanged TT₄ levels and a reduced TT₃ at day one after thyroid resection of patients with thyrotoxicosis.

The fate of circulating Tg is not clarified. From animal experiments, Taura et al. (1986) concluded that thyroid hormones were released from Tg within few hours by hydrolization in extra-thyroidal tissue. During our studies with thyroid resection, serum Tg levels showed a high and prompt rise with a mean peak value of 26 nmol/l. It is known that Tg from euthyroid persons contains approximately 2.5 mol T₄ per molecule, but treatment with thioureia drugs reduces this ratio to 0.5, whereas the molar ratio of T₃/Tg is not significantly changed (0.18 and 0.15 respectively) (Izumi & Larsen 1977). In the present study we failed to demonstrate any significant increase in either T₄ or T₃ levels following the Tg peak in serum. On the contrary, a decline in T₃ was measured. The discrepancy between the rat experiments and the present human study could be due to differences in Tg iodination in the rats and the antithyroid drug treated patients and to differences in the peripheral metabolism of Tg, which is yet not fully clarified (Izumi & Larsen 1978; Feldt-Rasmussen et al. 1978; Unger et al. 1980; Tatumi et al. 1979; Taura et al. 1986).

Several investigators have reported on changes of serum thyroid hormone concentrations in rela-
tion to non-thyroidal surgery (Kirby et al. 1973; Burr et al. 1975; Adami et al. 1978; Chan et al. 1978; Hagenfeldt et al. 1979; Kehlet et al. 1979; Prescott et al. 1979). A consistent finding in all studies was a rapid decline in serum TT$_3$ concentration beginning during operation combined with a concomitant rise in rT$_3$ level. The reciprocal changes of these two variables normalized within a few days after the surgical trauma. As for serum TT$_4$ and TSH, the results varied slightly probably due to differences in study design. The changes, however, were not essential.

In the present study, the changes in concentration of TT$_3$ and rT$_3$ during the operation are essentially similar to the pattern found in relation to non-thyroidal surgery. Reciprocal alterations in serum concentrations of TT$_3$ and rT$_3$, respectively, appeared promptly, whereas very little happened with regard to FT$_4$I and TSH levels. Postoperatively, however, the patterns differed. The significantly lowered values of serum TT$_3$ and FT$_4$I after thyroid surgery and the pronounced elevated TSH level observed were ascribed to the considerable reduction in thyroid mass.

Thyrotoxic crisis, although seldom nowadays, is an exceedingly serious complication to thyroid resection for thyrotoxicosis. Excessive thyroid hormone secretion is presumed to be part of the underlying disturbance, but a satisfactory understanding of the pathogenesis has not yet been attained (Hedge 1969; Mackin et al. 1974; Brooks & Waldstein 1980). Thyrotoxic crisis developing in the course of thyroid resection presents itself usually within a few hours after surgery (Ransom & Bayley 1934; Thompson & Fry 1964). To our knowledge, no specific thyroid hormone studies are available with reference to a relationship between total or free hormone concentrations and initiation of thyrotoxic crisis. Our presumption that the pronounced Tg release during thyroid surgery could give rise to high thyroid hormone values in serum and thereby forming part of the pathogenesis to thyroid storm was not confirmed.

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