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Thyroid-stimulating Hormone (TSH) Suppression in Differentiated Thyroid Carcinoma: Combined Treatment with Triiodothyronine and Thyroxine

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L-THYROXINE (THYR) is standard therapy in patients with differentiated thyroid carcinoma (DTC) after thyroidectomy and radioiodine ablation, not only to maintain euthyroidisms, but also to suppress thyroid-stimulating hormone (TSH), avoiding undue stimulation of tumour growth [1–5]. THYR withdrawal is mandatory once or twice a year to perform diagnostic 131-I total body scans (TBS) or radiodine treatments. When THYR treatment is recommenced, delay in TSH suppression, despite rapid clinical euthyroidism, has been demonstrated, even with high doses of THYR [6]. This is a limitation of treatment with THYR alone. Octreotide, in addition to THYR, for the first month significantly enhances TSH inhibition, reducing the period of elevated TSH levels, although not causing immediate inhibition of TSH [7]. However, octreotide administration is too expensive and impractical for routine clinical use. This study evaluates the effects of triiodothyronine (TRID) in association with THYR to reduce the period of inappropriate high TSH levels.

Short-term TSH suppression was evaluated in 60 patients with DTC after TBS and hormonal suppressive therapy had recommenced. Patients were divided into 6 groups of 10: Group 1 received 100 μg of THYR alone; Group 2 received 100 μg of THYR plus 20 μg of TRID; Group 3 received 100 μg of THYR plus 40 μg of TRID; Group 4 received 150 μg of THYR alone; Group 5 received 150 μg of THYR plus 20 μg of TRID; and Group 6 received 150 μg of THYR plus 40 μg of TRID. After a month of combined treatment, TRID administration was withdrawn and only THYR was maintained. Serum TSH, T3 and T4 were measured on the day of TBS (day 0) and after 7, 14, 21, 30, 45, 60 and 90 days. Serum T3 and T4 were assayed by specific RIAs (Radim), while those of TSH by an ultrasensitive immunoradiometric assay (Byk-Mallinckrodt). The significance of the differences between mean TSH values were evaluated by the Student's *t*-test.

The pattern of TSH inhibition was significantly different in the groups treated with THYR alone (Groups 1 and 4) compared with those with combined treatment (Figure 1). A rapid decrease of TSH serum levels was observed in patients receiving TRID (Groups 2 and 3 versus 1: $P < 0.01$ at 14, 21, 30 days; Group 5 versus 4: $P < 0.01$ at 7, 14 days and $P < 0.05$ at 21, 30 days; Group 6 versus 4: $P < 0.01$ at 7, 14, 21 days and $P < 0.05$ at 30 days). Serum T4 and T3 increased progressively after the beginning of hormonal treatment, reaching normal values in 14–20 days (Groups 1 and 4) or in 7 days in patients receiving 20 μg of TRID (Groups 2, 5; Table 1). In patients receiving higher TRID doses (40 μm, Groups 3 and 6), mean serum T4 remained normal, but mean serum T3 increased to the upper limit of the normal range after 21 days in Group 3 and after 7 days in Group 6. In all patients, T3 serum values quickly returned to normal after TRID administration was withdrawn. No relevant cardiovascular side effects were observed.

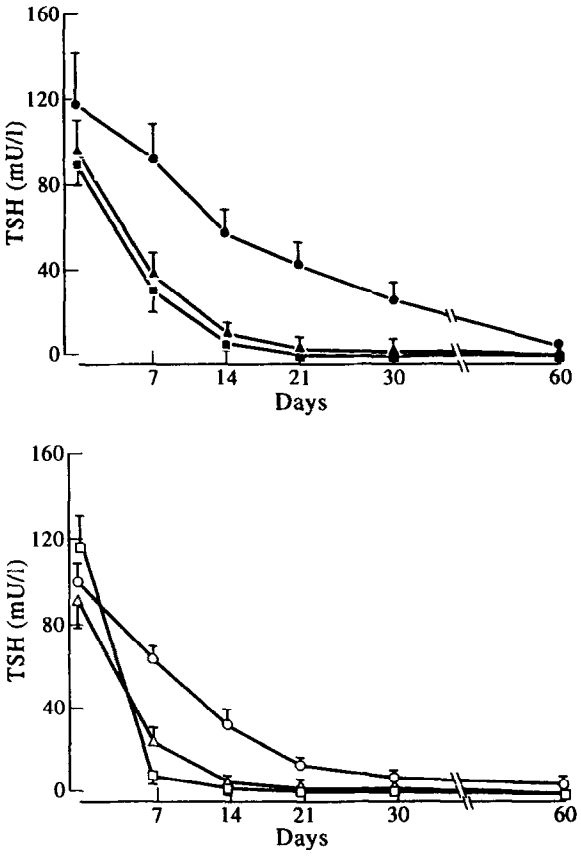

Figure 1. Mean serum TSH levels and SEM in six groups of patients with differentiated thyroid carcinoma after hormonal therapy was recommenced. Top panel: Group 1, 100 μg of THYR alone (circles); Group 2, 100 μg of THYR plus 20 μg of TRID (triangles); Group 3, 100 μg of THYR plus 40 μg of TRID (squares). Bottom panel: Group 4, 150 μg of THYR alone (circles); Group 5, 150 μg of THYR plus 20 μg of TRID (triangles); Group 6, 150 μg of THYR plus 40 μg of TRID (squares).

Thus, the addition of TRID to conventional therapy with THYR in patients with DTC greatly reduces the period of elevated TSH levels, and low TRID doses (20 μg) are more effective for TSH inhibition than augmentation of the THYR dosage. The schedule of the combined treatment is simple, inexpensive and has no discomfort or side effects for the patients. Significantly elevated T3 levels, associated with combined treatment, are transitory and have no relevant cardiovascular side effects.

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Table 1. Mean serum T3 and T4 levels and SEM (in parentheses) in six groups of patients with differentiated thyroid carcinoma after hormonal therapy recommenced. Normal values for T3 are 60–200 ng/dl and for T4 5–11.8 μg/dl

Days	0	7	14	21	30	60
T3						
Group 1	37.5	57.3	66.4	80.9	97.4	125.7
	(3.8)	(9.4)	(8.4)	(7.8)	(6.1)	(10.4)
Group 2	44.8	104.8	132.5	137.3	147.8	148.1
	(6.5)	(8.3)	(11.5)	(9.5)	(9.6)	(10.4
Group 3	45.7	150.0	173.8	177.0	214.3	145.0
	(5.3)	(14.9)	(17.8)	(13.6)	(22.3)	(10.2)
Group 4	30.6	63.1	93.9	112.0	119.1	139.7
	(38.0)	(8.4)	(11.2)	(8.2)	(6.2)	(7.1)
Group 5	38.9	137.5	172.0	190.0	186.0	169.0
	(5.0)	(20.4)	(10.7)	(18.6)	(13.0)	(8.8)
Group 6	32.1	215.0	228.7	222.5	206.5	151.0
	(2.8)	(20.3)	(20.4)	(17.2)	(7.7)	(8.8)
T4						
Group 1	0.6	3.2	5.1	6.8	8.0	10.4
	(0.1)	(0.5)	(0.5)	(0.5)	(0.5)	(0.6)
Group 2	2.0	6.1	7.0	7.1	7.8	10.5
	(0.4)	(0.4)	(0.2)	(0.3)	(0.4)	(0.3)
Group 3	2.6	5.5	7.3	7.7	9.0	10.4
	(0.5)	(0.5)	(0.7)	(0.6)	(0.5)	(0.4)
Group 4	1.1	5.5	8.3	10.2	10.7	13.9
	(0.1)	(0.7)	(0.9)	(0.9)	(0.8)	(1.0)
Group 5	3.3	8.0	11.1	11.5	11.4	12.8
	(1.2)	(1.1)	(0.8)	(0.8)	(0.5)	(0.4)
Group 6	1.8	6.6	8.8	10.1	10.5	14.1
	(0.3)	(0.5)	(0.8)	(0.9)	(0.5)	(0.8)

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Prognostic Significance of Phagocytic Functions in Breast Cancer Patients

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THE ROLE of immunocompetence in the prognosis of breast cancer has been widely examined, but to date no series of practical immunological tests has been identified which clearly permits accurate prediction of survival [1–3]. In this study, preliminary results of evaluation of prognostic significance of phagocytosis, the most important host defence mechanism, are presented. Using an acridine orange method described previously [4] and viable yeast cells as targets, the phagocytic activity (% of phagocytic cells), in addition to ingestion and intracellular killing abilities of peripheral blood granulocytes and monocytes, were determined in 66 patients (mean age 61 years) with ductal invasive breast cancer, clinical stages I, II and III (38, 40 and 6%, respectively). Assessments were made after radical mastectomy, but before proceeding with any other therapy, and repeated for a group of 36 age- and sex-matched healthy volunteers. Results were analysed using the Mann–Whitney U test. Granulocyte ingestion ($P=0.001$), granulocyte microbicidity ($P<0.009$) and monocyte microbicidity ($P=0.039$) were decreased in the patient group compared with normal values. After a 3-year follow-up, 8 patients (group B) developed distant metastases (2 liver, 2 lung, 4 bone), while the other 58 remained free of metastases (group A). Retrospective analysis of phagocytic functions determined at the beginning of the follow-up period (i.e. at the time when all patients were free of distant metastases) showed differences between these two groups. Granulocyte phagocytic activity in group B was decreased in comparison with group A ($P=0.057$). Monocyte phagocytic activity in group B was also decreased, although the difference was less significant ($P=0.103$). Further differences appeared in the monocyte intracellular killing capacity, which

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