Original Article

Is 3–4 Weeks Required for TSH to Rise Post Thyroidectomy? A prospective Study and Discussion of its Implications on Patient Care

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Abstract

Context: In patients with differentiated thyroid cancer (DTC), for the purpose of radioiodine (^{131}I) whole-body scan and treatment of remnant, or residual tumor, or metastatic disease, thyroid hormone withdrawal remains the standard approach for raising thyroid-stimulating hormone (TSH) levels to ensure adequate radioiodine uptake. Thyroid hormone is withdrawn 3–4 weeks prior radioiodine therapy (RAIT) to allow the serum-TSH concentration to rise to above 25–30 mU/L. **Aims:** We studied the time taken for TSH to rise in 40 patients after total thyroidectomy operated for DTC. **Settings and Design:** Prospective observational study. **Methods and Materials:** 40 patients with proven differentiated thyroid cancer attending a tertiary care center were studied. **Statistical Analysis Used:** Data was analyzed by using SPPSS software for windows (version 15, SPSS Inc., Chicago, USA). **Results:** After performing preoperative TSH in all patients excluding preoperative TSH elevation, it was planned to collect weekly postoperative samples till TSH ≥30. The mean (standard deviation, SD) age of the cohort was 40 (13) years with 35 females (88%) and their mean (SD) preoperative TSH was 3.6 (1.35) mIU/L. At the end of the first week postoperatively, the mean TSH of the cohort was 24.25 (6) with 8 patients (20%) achieving the cut-off of TSH ≥30 mIU/L and 30 patients (75%) achieving TSH level ≥20 mIU/L. At the end of the second week, the mean TSH was 53 (17) with all patients (100%) achieving a TSH level >30 mIU/ml. **Conclusions**: An iodine whole-body scan can be performed in 10–14 days after total thyroidectomy instead of the usual wait time of 4 weeks. This could improve patient QOL and avoid complications related to prolonged hypothyroidism.

Keywords: Whole-body iodine scan, thyroid cancer, TSH withdrawal scan

Introduction

Radioiodine (^{131}I) is given under TSH stimulation to perform a whole-body scan (WBS) or ablate any remaining cancer cells and thyroid tissue in patients with differentiated thyroid cancer (DTC) after total thyroidectomy. Sodium-iodide symporter (NIS) expression at the plasma membrane in the thyroid follicular cell constitutes the basis of RAIT for hyperthyroidism and DTC.[1,2] Despite the physiological and clinical relevance of NIS plasma membrane expression, less is known regarding the molecular mechanisms underlying NIS transport to the plasma membrane. TSH constitutes the primary regulator of NIS expression in the thyroid follicular cell by not only stimulating NIS expression at the transcriptional level, but it is also required at post-translational levels for targeting NIS to, and/or retaining it, the plasma membrane.[1,2]

In the setting of ^{131}I treatment of remnant, or residual tumor, or metastatic disease, thyroid hormone withdrawal remains the standard approach in raising TSH levels for adequate radioiodine uptake. As a convention with the aim to reduce circulating free thyroxine (T4) levels below the normal range,

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thyroid hormone is withdrawn 3–4 weeks prior RAIT.[3] After thyroidectomy or cessation of T4 therapy, the patient's serum-T4 concentration should decline sufficiently to allow the serum-TSH concentration to rise above 25 to 30 mU/L.[4] As a consequence, patients with DTC may be exposed to repeated and prolonged periods of hypothyroidism that affect their quality of life and may increase the potential for tumor growth. To minimize the severe discomfort due to gross hypothyroidism, recombinant human (rhTSH) has been used for enhancing radioiodine uptake while the patient is continued on thyroxine replacement. The cost of rhTSH therapy precludes routine use in DTC patients, especially, in a resource-constrained setting such as India. In some centers, patients are placed on 50% dose of thyroxine while in others, Triiodothyronine (LT3) (not easily available in India) is used during the TSH withdrawal protocols. Previous studies have shown that there is an exponential rise of TSH after thyroidectomy or thyroid hormone withdrawal and TSH rise occurred much earlier than 4 weeks.[5-7] In this case one might able to expedite the ^{131}I-WBS scan and therapy in these patients and minimize their morbidity related to hypothyroidism.

Aims

To study the time taken for TSH to rise after total thyroidectomy in patients operated for DTC.

Subjects and Methods

Following the Institutional review board (IRB) and ethics committee approval, we were able to recruit 40 patients, undergoing total or near-total thyroidectomy, for DTC which was confirmed by histopathology. All consecutive patients who underwent total thyroidectomy for known differentiated thyroid cancer (based on fine-needle aspiration cytology, FNAC) were explained about the study. Of those patients, who gave informed written consent and patients whose histopathology confirmed differentiated thyroid cancer (papillary and follicular thyroid cancer, PTC) and planned for RAIT/scan were included in the study. Postoperative blood samples for TSH were collected weekly until a result of TSH ≥30 was obtained. TSH was performed using electro-chemiluminescence assay. Free thyroid hormones were not done postoperatively. All surgeries were done by a single surgeon (Author DS).

Sample Size and Statistics

Considering TSH elevation after thyroidectomy or thyroid hormone withdrawal, previous studies have studied sample sizes ranging from 13–25[5-7] and TSH levels were checked once a week or once in 3–4 days. Data are presented as mean ± SD. Mann-Whitney test was used for comparison among continuous variables. Statistical analysis was done in Microsoft Excel (version Office 365) and SPSS version 15.

Results

The data of all the patients are shown in Table 1. The mean (SD) age of the cohort was 40 (13) years with 35 females (88%) and their mean (SD) preoperative TSH was 3.6 (1.35) mIU/L. Of the 40 subjects, 39 had papillary thyroid cancer (PTC) wherein 32 had classical variant and 7 had follicular variants of PTC and one had follicular thyroid cancer (FTC). Of those with 39 PTC, 20 had a prophylactic central compartment lymph node dissection (CCLND), 10 had therapeutic CCLND and 9 did not undergo CCLND. Only one patient of FTC had total thyroidectomy. Of those 10 subjects who underwent therapeutic CCLND, 6 underwent therapeutic lateral lymph node dissection (4 unilateral and 2 bilateral). None had distant metastatic disease at the time of diagnosis and during the initial whole body-iodine scan. Of the 40 patients included, 8 had high TPO levels. Of those 8 patients, 5 had TSH level <10 mIU/l and were on thyroxine replacement. But during surgery, all the 40 patients were euthyroid and TSH was within normal reference range. At the end of the first week postoperatively, the mean TSH of the cohort was 24.25 (6) with 8 patients (20%) achieving the required cut-off of TSH ≥30 mIU/L and 30 patients (75%) achieving TSH level ≥20 mIU/L. The 8 patients (6 females) whose levels rose to ≥30 mIU/L by the end of the first week, had a mean age of 42 (14) years, a mean preoperative TSH of 4 (1.45) which was not statistically different from those whose level did not rise [mean TSH of 3.5 (1.5, $P = 0.4$)]. At the end of the second week, the mean TSH was 53 (17) with all patients (100%) achieving a TSH level >30 mIU/L.

Discussion

We noted that it took between 7–14 days to achieve a TSH level of ≥30 mIU/L post-thyroidectomy. According to recommendation 53 from the ATA guidelines,[3] "If thyroid hormone withdrawal is planned prior RAIT or diagnostic testing, levothyroxine (LT4) should be withdrawn for 3–4 weeks. LT3 may be substituted for LT4 in the initial weeks and LT3 should be withdrawn for at least 2 weeks. Serum TSH should be measured prior radioisotope administration to evaluate the degree of TSH elevation (strong recommendation, moderate-quality evidence). A goal TSH of >30 mIU/L has been generally adopted in preparation for RAIT or diagnostic testing". However these data are based on the previous study where TSH was initially measured 3 weeks after the surgery and did not look in sequential TSH measurements after thyroidectomy[8] and ever since this time duration of 3–4 weeks has been followed as a convention in the Nuclear Medicine Departments of the institutes and hospitals. There are three studies in the literature that clearly suggest TSH elevation occurs exponentially after thyroidectomy or thyroid hormone withdrawal. In a study by Serhal *et al.*, serum-TSH concentrations reached >30 mU/L 8–26 (mean ± SD, 14.2 ± 4.8) d after thyroidectomy or 9–29 (18.1 ± 4.1) d after T4 withdrawal.[5] That level of TSH elevation was achieved 18 d after thyroidectomy and 22 d after T4 withdrawal in more

Table 1: Data of the 40 patients with presentation characteristics and type of surgery and final histopathology

n	Age (yrs)	Sex	Preop TSH	Mode of Presentation	Type of Surgery	TSH 1 (7 days postop)	TSH 2 (14 days postop)	TSH 3 (21 days postop)	TSH 4 (28 days postop)	FINAL HPE
1	26	f	3.2	STN	TT	18	40	70	>100	PTC
2	45	f	2.1	MNG	TT	27	70	>100	>100	PTC
3	36	f	1.8	STN	TT+CCLND	23	36	82	>150	PTC
4	62	f	4.2	STN with lymph nodes	TT+CCLND+left MRND	21	46	89	>150	PTC
5	51	m	3.9	STN	TT	27	56	>100	>100	PTC
6	32	f	4.1	MNG	TT+CCLND	20	45	92	>150	FVPTC
7	41	f	2.5	STN	TT+CCLND	19	38	85	108	PTC
8	28	f	1.9	STN	TT+CCLND	26	32	72	120	PTC
9	51	f	4.6	STN	TT+CCLND	22	42	82	128	PTC
10	42	f	5.2	STN	TT+CCLND	26	38	72	130	FVPTC
11	40	m	3.6	MNG	TT+CCLND	19	41	68	124	PTC
12	32	f	4.1	MNG	TT	22	37	80	132	PTC
13	41	f	2.9	STN with lymph nodes	TT+CCLND+B/L MRND	26	42	100	>140	PTC
14	49	m	3.2	STN	TT+CCLND	30	40	82	>100	PTC
15	42	f	1	MNG	TT	19	38	59	82	FVPTC
16	19	f	2.1	MNG	TT	16	60	78	126	PTC
17	22	f	1.8	STN with lymph nodes	TT+Rt MRND	22	42	68	80	PTC
18	71	f	5.4	STN	TT+CCLND	30	48	60	89	PTC
19	18	f	0.9	MNG	TT	28	51	72	>100	FVPTC
20	45	f	4.8	MNG	TT+CCLND	26	60	78	94	PTC
21	42	f	3.8	STN	TT	18	42	76	>100	PTC
22	32	f	4.1	MNG with lymph nodes	TT+CCLND+left MRND	23	58	90	>100	PTC
23	42	m	1.6	MNG	TT	30	44	80	>100	PTC
24	31	f	4.9	STN	TT+CCLND	31	89	>100	>100	PTC
25	50	f	2.9	STN	TT	36	102	>150	>150	FTC
26	32	f	6.1	STN	TT+CCLND	38	78	>150	>150	PTC
27	38	f	4.1	MNG	TT+CCLND	40	68	>100	>100	PTC
28	62	f	5.9	MNG	TT+CCLND	19	58	>100	>100	PTC
29	31	f	3.7	MNG with lymph nodes	TT+CCLND+B/L MRND	24	64	98	>150	PTC
30	30	f	5.2	STN	TT+CCLND	29	72	>150	>150	PTC
31	56	f	4.5	STN	TT+CCLND	21	34	68	130	PTC
32	49	m	2.9	MNG	TT+CCLND	19	40	>100	>100	FVPTC
33	28	f	4.8	STN	TT+CCLND	22	32	80	>100	PTC
34	39	f	5.1	STN with lymph nodes	TT+CCLND+left MRND	18	42	79	>100	FVPTC
35	48	f	1.8	MNG	TT+CCLND	21	38	>100	>100	FVPTC
36	18	f	3.7	STN	TT+CCLND	22	48	>100	>100	PTC
37	28	f	4.1	MNG	TT+CCLND	31	41	>100	>100	PTC
38	41	f	3.7	MNG	TT+CCLND	24	38	69	98	PTC
39	49	f	2.9	STN	TT+CCLND	15	38	55	77	PTC
40	61	f	5.1	STN	TT+CCLN D	22	31	49	94	PTC

STN: Solitary Thyroid nodule; MNG: Multinodular goiter; TT: Total Thyroidectomy; CCLND: Central Compartment Neck Dissection; MRND: Modified Radical Neck Dissection; PTC: Papillary thyroid cancer (Classic); FVPTC: Follicular Variant Papillary thyroid cancer; FTC: Follicular Thyroid cancer, Post-op: Postoperative, Preop: Preoperative

than 95% of patients. In another study by Leboeuf *et al*.,[6] the time needed to reach a TSH level >30 mUI/L was 17 ± 9 d and was significantly longer in patients on T3 (32 ± 4 d; $P = 0.006$). Liel *et al.* showed that in 13 patients on suppressive doses of thyroxine, on 15 separate occasions, baseline TSH levels were between 0.01 and 0.4 mIU/L.[7] The mean interval required to reach the target TSH concentration of at least 30 mIU/L was 17 days (95% CI 15–19; range 11–28 days). Our study replicates the same finding that by 2 weeks wherein all patients attained target TSH >30mIU/L.

This poses the question; do patients really have to wait for 3–4 weeks for their radioiodine scan? TSH constitutes the primary regulator of NIS expression in the thyroid follicular cell by not only stimulating NIS expression at the transcriptional level, but it is also required at post-translational levels for targeting NIS to, and/or retaining it at, the plasma membrane. The molecular mechanism regulating TSH-stimulated NIS transport to, retention at, and removal from the plasma membrane remains unknown. In functional thyroid cells (FRTL-5) of rat, immunofluorescence analysis demonstrated that after TSH withdrawal, NIS molecules located in the plasma membrane are redistributed to uncharacterized intracellular compartments.[9] TSH may also play a role in phosphorylation of proteins and the activation of several protein kinases, which might constitute a post-translational modification involved in the NIS intracellular transport process.[10] Thus it may not be for "TSH elevation" that we are waiting for but for the complete effect of the "TSH elevation on the NIS expression".

DTC often exhibit reduced (or even undetectable) iodide transport compared with normal thyroid tissue, and they are diagnosed as cold nodules on thyroid scintigraphy. Hence one may argue about the prolonged wait for a good 4 weeks to improve NIS expression on the follicular cells of the residual thyroid and cancer cells, which needs activation of intracellular protein machinery after elevations of TSH and its action on TSH receptor. However rhTSH-based protocols are done in a very short time of 2–5 days after administration of rhTSH with equal diagnostic and therapeutic efficacy, thus reducing the need for prolonged wait.

Based on our study we suggest a waiting time of 10–14 days after thyroidectomy by a high-volume thyroid surgeon for iodine scan rather than conventional wait time of 3–4 weeks. The strength of the study was a single surgeon (author DS), who operated all the patients, so the degree of remnant thyroid affecting the TSH levels was consistent. The limitation of our study is that we did not include patients on suppressive doses of thyroxine to see when they attain TSH level ≥30 mIU/L after cessation of T4 therapy. We also did not have sufficient people for comparison with or without TPO positivity—to observe if this was a factor in the rate of rising TSH. We also have not compared ^{131}I-WBS at an earlier period (done at 10–14 days) with the traditional scan at the end of 4 weeks to observe if it made any difference in the intensity of uptake.

Conclusion

^{131}I-WBS can be performed in 10–14 days after total thyroidectomy instead of the usual wait time of 4 weeks. This could improve patient QOL and avoid complications related to prolonged hypothyroidism.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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