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Three-week thyroxine withdrawal thyroglobulin stimulation screening test to detect low-risk residual/recurrent well-differentiated thyroid carcinoma[ø]

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ABSTRACT. Measurement of serum TSH-stimulated thyroglobulin (Tg) is recognized as a sensitive method for detecting residual/recurrent well-differentiated thyroid carcinoma (WDTC) in patients previously treated by surgery and radioactive iodine (RAI) ablation therapy. WDTC patients who have an undetectable serum Tg on thyroid hormone therapy (THT) in the absence of Tg-antibody interference are considered to be at low risk for residual/recurrent disease. Traditional management has been to withdraw T_4 for 4-6 weeks or T_3 for 2 weeks to stimulate endogenous TSH. However, this prolonged THT withdrawal induces hypothyroidism and its concomitant morbidity. In the present study, we assess the efficacy of shortening the time of T_4 withdrawal to only 3 weeks for detecting residual/recurrent WDTC as a sufficient serum TSH stimulus for obtaining a positive serum Tg result without a routine diagnostic whole body scan (WBS). Additionally, we have evaluated the impact of such a T_4 withdrawal interval on quality of life and loss of employment time. A total of 181 patients with WDTC selected for study had previously been treated with a bilateral surgical thyroidectomy followed by RAI ablation therapy (average post-surgery to follow-up interval of 10.8 yr). All of the cohort had an undetectable (<1 μg/l) serum Tg on THT without Tg-antibody interference. Serum TSH and Tg were measured before and after cessation of T_4 therapy for 3 weeks. A serum Tg ≥2 μg/l was considered positive for residual/recurrent disease. A quality of life questionnaire [Short-Form 36 (SF-36)] was administered before withdrawal, at peak TSH and after resumption of therapy. From the completed SF-36 questionnaires, the overall degree of functional impairment was not severe and did not result in loss of employment time. Moreover, this protocol identified three possible responses to the 3-week T_4 withdrawal interval as follows: a) serum Tg undetectable with TSH ≥25 mIU/l (~75% of total cohort); b) serum Tg ≥2μg/l (~10% of total cohort) which will require further investigation and treatment for residual/recurrent disease; c) undetectable serum Tg with inadequate TSH rise (~15% of total cohort), which will require TSH stimulation by either longer T_4 withdrawal or recombinant human TSH to exclude residual disease. We conclude that a stimulated serum Tg test performed 3 weeks after T_4 withdrawal is a simple and cost-effective first-line screening test with minimal morbidity which is sufficient to evaluate low-risk WDTC patients for recurrent/residual carcinoma.

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INTRODUCTION

Nearly 16,000 people in the United States are diagnosed with thyroid cancer each year (1). Papillary and follicular carcinomas account for most of these cases. Although well-differentiated thyroid carcinoma (WDTC) is considered one of the most curable cancers, it requires life-long monitoring because it has been known to reappear many decades after the initial diagnosis, with the highest risk of recurrence occurring within the first 10 yr (2). Diagnostic monitoring of patients

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with WDTC aims at detecting local or distant residual/recurrent thyroid carcinoma (3).

In the past, whole body scanning (WBS) and measurement of serum thyroglobulin (Tg) levels have been recommended as the most important routine diagnostic tests to detect recurrent or residual WDTC. Although the combination of WBS and Tg testing after T_4 withdrawal to stimulate endogenous TSH can theoretically enhance detection, the diagnostic superiority of serum Tg over WBS has been repeatedly demonstrated in those WDTC patients who are Tg-antibody negative, thereby supporting the conclusion that a stimulated serum Tg test is a more sensitive and cost-effective diagnostic test than a WBS (2, 4-10). Following total thyroidectomy and adequate radioactive iodine (RAI) remnant ablation, the detection of a positive serum Tg value while on sufficient thyroid hormone suppression therapy to produce an undetectable serum TSH indicates a high risk for recurrent/residual disease and the immediate need for further localization studies, as well as probable surgical and radioiodine interventional therapy. In contrast, patients with undetectable serum Tg while on adequate thyroid hormone therapy (THT) are at low risk for residual WDTC. Since the sensitivity of serum Tg test as a marker for residual disease is known to be enhanced by endogenous TSH stimulation, patients who are at low risk while on T_4 or T_3 therapy may continue to have some residual disease that could be evident upon further testing in the presence of increased serum TSH levels (3). The sensitivity of a serum Tg test as a marker for residual disease is enhanced by endogenous TSH stimulation. However, serum Tg measurements after withdrawal from T_4 for 4-6 weeks or T_3 for 2 weeks have been documented to cause prolonged and severe hypothyroidism, and is accompanied by significant morbidity, reduced quality of life and loss of work time (11, 12). To minimize the adverse effects associated with currently recommended thyroid hormone withdrawal protocols, we have evaluated in the present report the efficacy of utilizing a shorter (3-week) T_4 withdrawal interval for the detection of residual/recurrent thyroid carcinoma in a low-risk WDTC study cohort by the measurement of a stimulated serum Tg without a diagnostic WBS. Also, we have assessed the impact of this screening test on quality of life and loss of work time.

MATERIALS AND METHODS

Patient characteristics and inclusion criteria

With informed consent, WDTC patients who had been previously treated with total or near-total thyroidectomy as well as one or more doses of RAI ablation therapy were selected for the study. All patients had undetectable serum Tg (<1 mg/l) while on T4 therapy and were negative for an interfering positive serum Tg-antibody by two different methods (8) and therefore considered to be at low-risk. Th therapy was administered in accordance with current principles to suppress TSH whenever possible according to the stage of disease and clinical presentation. Conversely, patients with a detectable serum Tg while on T4-TSH suppression therapy were considered to be at high risk and excluded from our study. The study cohort consisted of 181 low-risk WDTC patients (152 females and 29 males). The average time of follow-up from initial surgery was 10.8 yr (range 2 to 37.8 yr). The mean age of the study cohort was 43 yr (range 16-77 yr) at the time of initial surgical pathology diagnosis. The University of Chicago WDTC Staging System (13) used to classify the severity of disease and the distribution of stages within the study cohort is outlined in Table 1. Cumulative doses of RAI ranged from 25-571 mCi, with the average dose varying with each stage: stage I – 99 mCi (no.=112), stage II – 188 mCi (no.=49), stage III – 232 mCi (no.=13) and stage IV – 571 mCi (no.=1); only 6 patients received less than 60 mCi. The entire study cohort had a previously documented post-radioactive 131I iodine therapy WBS that had minimal-to-absent thyroid bed uptake and no evidence of extra-thyroidal uptake.

Table 1 - *Distribution of well-differentiated thyroid carcinoma (WDTC) stages (upper panel) and pathologies (lower panel) at diagnosis for the study cohort.*

WDTC staging distribution		
Stage	No. of patients	%
I	118	65.19
II	49	27.07
III	13	7.18
IV	1	0.55
Distribution of WDTC pathology diagnoses		
Pathology	No. of patients	%
Papillary	126	69.61
Follicular	18	9.94
Mixed	30	16.57
Hurthle/tall cell variant	7	3.87

Study protocol

Serum TSH, Tg and Tg-antibody levels were assayed prior to T_4 withdrawal and repeated 22 days later. T_4 therapy was resumed thereafter in combination with tapering doses of T_3 (Fig. 1). The Short-Form 36 (SF-36) questionnaire (14, 15) was administered to those with no language comprehension barrier at three time points: prior to commencing the study (day 1), upon completion of the 3-week withdrawal from T_4 (day 22) and 4 weeks after resumption of the T_4/T_3 combination therapy (day 51). Based on previous published experience in other centers (5, 6, 10, 16) and our own personal observations (unpublished) on the poor sensitivity of WBS in detecting metastatic thyroid cancer (except perhaps by a WBS performed following high-dose therapeutic RAI), we and many

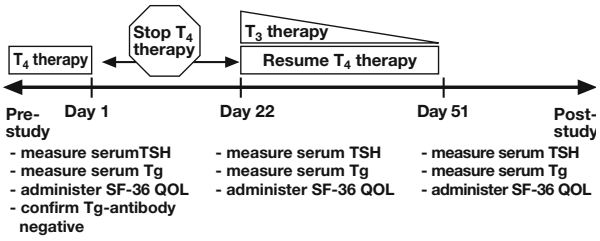

Fig. 1 - *Outline of study protocol. Day 1 corresponds to the cessation of T_4 therapy and administration of the first voluntary Short-Form 36 (SF-36) quality of life (QOL) questionnaire. Day 22 indicates the peak hypothyroid state and resumption of T_4 with tapering T_3 therapy. The second and third voluntary SF-36 QOL questionnaires are administered on days 22 and 51.*

others have abandoned routine diagnostic WBS as an essential detection test for residual/recurrent WDTC, in favor of only serum Tg screening. Accordingly, to eliminate further inconvenience, morbidity and cost, the current study group was not subjected to routine diagnostic WBS and instead was monitored at 6-month intervals by serum Tg, neck ultrasound (US) and by other special procedures as indicated.

Serum TSH, Tg and Tg-antibody assays

All serum assays were performed at the Department of Clinical Biochemistry (Mount Sinai Hospital Laboratory, Toronto, ON, Canada). Serum Tg was measured by an immunoradiometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA) which utilizes the CRM-457 international Tg standard and has a lower detection limit of 0.9 µg/l. Serum Tg levels of ≥2 µg/l were considered positive for possible residual disease, while Tg levels of 1 µg/l (near the detection limit) were considered equivocal. Serum Tg antibody was considered to be negative for Tg assay interference when both <20 kIU/l by Immulite 2000, as well as <60 IU/ml by Pharmacia Tg antibody EIA Kit automated on a Personal Lab Analyser (BioChem ImmunoSystems Inc; Montreal, Canada). Serum TSH was assayed using a third-generation TSH immunometric assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA) with normal range of 0.5-5.0 mIU/l and a lower detection limit of <0.01 mIU/l.

Data analysis

All statistical tests were two-sided and the significance level (α) used was 0.05. SF-36 data were analyzed by the Wilcoxon signed rank test (15). Correlation was calculated using standard statistical analysis.

RESULTS

Serum TSH levels

Three weeks after T_4 withdrawal, the median TSH concentration rose to 45.2 mIU/l, while the mean was 54.5 mIU/l (range 3.01-212 mIU/l). Among the 181 patients, 150 (83%) had TSH levels ≥25 mIU/l (Fig. 2). Among the remaining 31 patients with a TSH rise below 25 mIU/l, 3 patients had elevated Tg, 2 of whom had disease later confirmed by histology. The median baseline serum TSH concentration was 0.19 mIU/l. While all of the study cohort had serum Tg values of <1 µg/l on entry to the study, baseline serum TSH levels just before T_4 withdrawal (day 1) varied from maximally suppressed (<0.01 mIU/l) to thyroid hormone replacement therapy levels (0.5-5.0 mIU/l), depending on the clinical presentation of the patients (age, cardiac disease, staging). However, no significant correlation was found between baseline (day 1) and peak serum TSH (day 22); a low baseline serum TSH (<0.01 mIU/l) did not significantly contribute to the number of patients who were observed to have a serum TSH rise that was <25 mIU/l. Moreover, no correlation was detected between the previous T_4

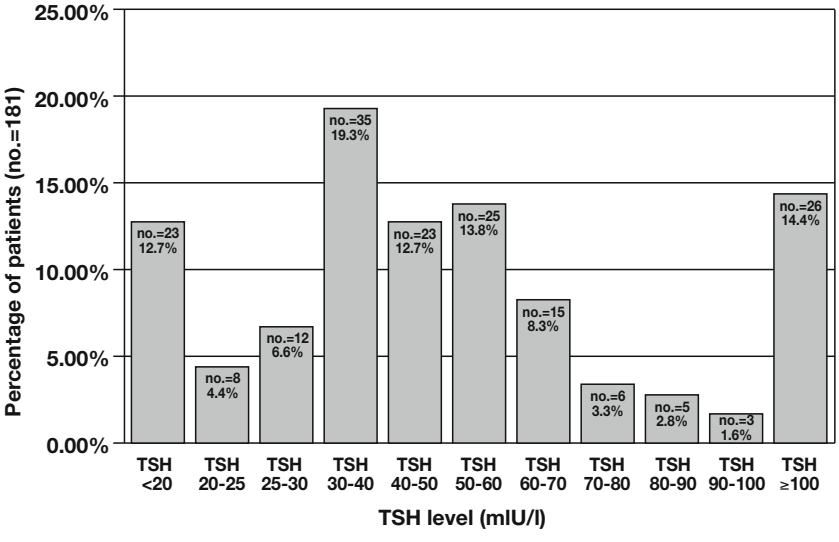

Fig. 2 - *Distribution of serum TSH levels after 22 day T_4 withdrawal.*

dose/kg body weight and either the observed serum TSH or Tg response. Also, none of these variables could be significantly correlated with a serum TSH at day 22 that was either greater or less than 25 mIU/l. Thus, neither a high T_4 dose prior to the withdrawal test, nor maximal baseline TSH suppression predicted either peak TSH values or positive Tg outcomes.

Serum Tg response

While on T_4 therapy, the baseline serum Tg levels of all patients were below the limit of Tg detection of 1 µg/l. After T_4 withdrawal, 15 of 181 (8%) patients were observed to have serum Tg levels ≥2 µg/l. Among these Tg positive subjects, the mean serum Tg level was 10 µg/l (range 2-35 µg/l) and the distribution of positive serum Tg based upon the WDTC presenting disease-severity classification was 3/118 (3%) Stage I, 12/63 (19%) Stage II-IV of whom 9/49 (18%) were Stage II, 2/13 (15%) were Stage III, and 1/1 (100%) was Stage IV. As expected, the highest positive serum Tg prevalence occurred in Stage II-IV (19%) compared to Stage I (3%) WDTC. While the mean serum TSH level in Tg positive patients was 54.5 mIU/l (range 3-110 mIU/l), it is of interest to note that 3 patients were Tg positive despite stimulated TSH levels less than 25 mIU/l. A summary of serum assay results, stage of WDTC and outcomes for these 15 patients is illustrated in Table 2. There was no significant statistical correlation observed between either basal TSH and peak Tg or peak TSH and peak Tg.

To our knowledge, there have been no patients with undetectable stimulated serum Tg test results who have had evidence clinically or by imaging of residual/recurrent disease detected despite continued regular follow-up of the study cohort that ranged from 0.7 to 3.2 yr (a median follow-up after the withdrawal screening test of 2.1 yr). Only one patient in this study with an undetectable serum Tg after T_4 withdrawal stimulation was initially considered to be a false negative. This patient had presented as high-risk Stage III tall-cell variant of papillary thyroid cancer that advanced to Stage IV without any detectable increase in serum Tg, despite an increase in serum TSH to 74.8 mIU/l after T_4 withdrawal (see Discussion). However, subsequent follow-up of this patient with apparent Stage IV metastatic lung disease revealed a adenocarcinoma of non-thyroidal origin, indicating that this apparently false negative result was incorrect. Over 95% of the study cohort who had an undetectable stimulated Tg result have continued to be monitored at regular intervals for 2 or more yr following the T_4 withdrawal Tg stimulation test. Examination of this cohort by clinical palpation, serum Tg, ultrasound, head/neck and chest CT as indicated for Stage II-IV subjects have failed to detect a post-T_4 withdrawal false negative test result or any definite evidence for residual/recurrent WDTC. To date we have not detected any now evidence for either a false negative or false positive result.

Table 2 - *Summary of the follow-up results for 15 patients with positive serum thyroglobulin (Tg). All serum Tg positive patients underwent further neck ultrasound (US)/computed tomography (CT) imaging, and a guided fine-needle aspiration biopsy and/or surgery were performed whenever feasible. Radioactive iodine therapy (RAI) was administered after repeat surgery and/or after positive non-radioisotope imaging results whenever possible. A whole body scan (WBS) was obtained only after RAI therapy.*

Pt no.	Sex	Age	Class	Pathology	TSH after	Tg after	Confirmed by
Tg ≥2, positive detectable Tg							
1	F	38	2	Papillary	42	2	Positive CT chest
2	F	55	3	Papillary	61	16	Positive neck US
3	F	33	2	Mixed	12	21	Not available
4	F	39	1	Mixed	24	10	Positive WBS
5	F	60	1	Papillary	43	3	Positive CT chest
6	F	16	4	Papillary	47	4	Positive WBS
7	F	55	3	Papillary	56	35	Positive histology
8	F	29	1	Papillary	54	2	Positive neck US
9	F	24	2	Papillary	44	2	Not available
10	F	56	2	Papillary	48	2	Not available
11	M	51	2	Papillary	25	26	Positive histology
12	M	34	2	Papillary	28	2	Positive histology
13	F	43	2	Papillary	3	3	Positive histology
14	F	25	2	Papillary	58	3	Positive neck US
15	F	25	2	Papillary	110	18	Positive CT neck

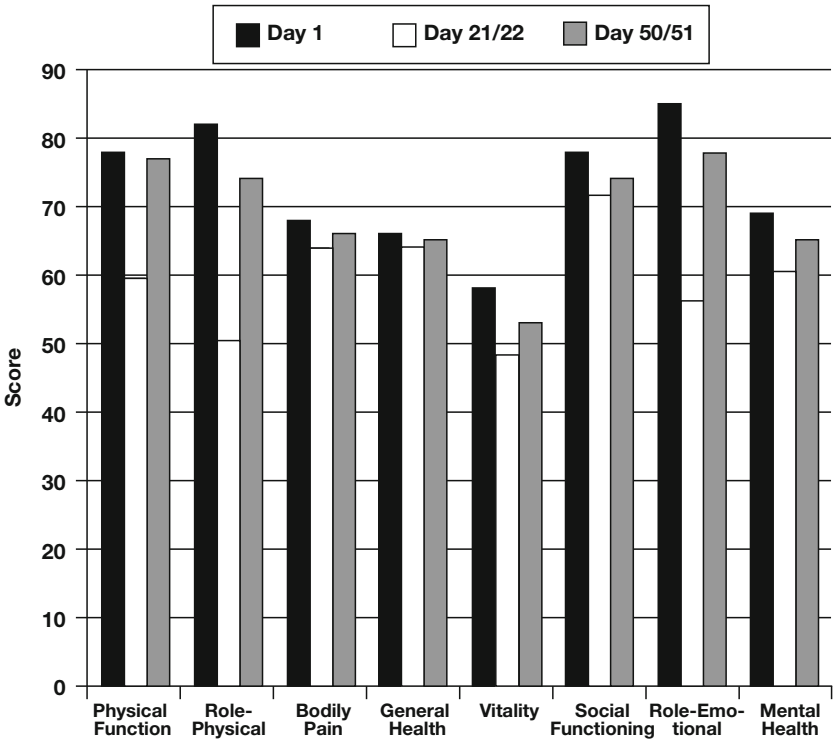

Fig. 3 - *Summary of Short-Form (SF-36) quality of life scores. Illustrated are the baseline (before T_4 withdrawal) scores for day 1, compared to peak hypothyroid state off L-T_4 therapy on day 22, and one month after resumption of T_4/T_3 combination therapy on day 51. Significant changes ($p<0.05$) were obtained from day 1 to day 22 in the Physical Function, Role-Physical, Vitality, Social Function, Role-Emotional and Mental Health categories. The changes observed for the Bodily Pain and General Health categories were not significant ($p<0.05$).*

SF-36 health survey results

Among 181 cohort patients, 72 subjects could not satisfactorily complete the questionnaire owing to language comprehension problems. Among the remaining 109 patients, 108 (99%) completed questionnaires corresponding to the first 2 phases of the study (i.e. impact of T_4 withdrawal) and 77 (71%) also completed questionnaires at the third time interval (day 51) to evaluate whether recovery occurred after T_4/T_3 therapy. In addition to the questionnaires, all patients underwent routine clinical examinations on day 22 after T_4 withdrawal and were asked to report any absence from work. Except for a follow-up visit to provide a blood sample and obtain instructions on resuming T_4/T_3 therapy, only one patient in the study reported more than 1 day of absence from work during the 22-day T_4 withdrawal interval. There was no significant change in the General Health and Bodily Pain categories. Relative to the general population, the SF-36 scores for the study group indicated that patient quality of life did not fall below 50% of the general population scores, with the exception of the Vitality category (Fig. 3). Based on a cut-off of 50% of the general population scores (15), the overall health of patients in the study group remained tolerable after 3 weeks of T_4 withdrawal. Although a statistical difference (range of p=0.001 to p=0.01 by paired t-test) in 6 out of 8 SF-36 categories was observed (Fig. 3) when comparing the results of the questionnaires administered before and after T_4 withdrawal, the morbidity was tolerable. Four weeks after resumption of T_4/T_3 therapy, quality of life returned to pre-withdrawal levels (i.e. no statistical differences were noted) for all categories (Fig. 3). Taken together, these results indicated that the 3-week T_4 withdrawal study induced a significant but modest impact of quality of life that was tolerated by the vast majority of patients without loss of work time, except for the day 22 visit for the serum sampling and T_4/T_3 replacement hormonal therapy instructions.

DISCUSSION

Since serum Tg can be synthesized by remnant WDTC cells and stimulated by increases in serum TSH (17), it can be a useful marker for residual/recurrent thyroid carcinoma when there is no Tg-antibody interference and a near-total surgical thyroidectomy and RAI ablation treatment have been performed. However, WDTC patients with residual/recurrent disease may not have a detectable level of serum Tg while on T_4-TSH suppression therapy owing to decreased TSH stimulation and a more rapid serum Tg metabolic clearance rate (6, 18-20).

A previous report had observed that while on TSH suppression therapy, up to 20% of patients were subsequently confirmed upon T_4 withdrawal to have unsuspected lymph node metastases and 5% were at risk of distant micrometastases (3). Remarkably, the results obtained in the current study are in striking agreement with this report (3), since the prevalence of a positive Tg among Stage II-IV study cohort patients was 19%, whereas the prevalence among Stage I patients was only 3%. Moreover, most patients with undetectable serum Tg after TSH stimulation were documented to be disease-free 20 yr after surgery and RAI therapy (3), thereby supporting the utility of this parameter as a prognostic indicator (3). Of the 15 patients found to be Tg positive in our study, 12 (80%) were later confirmed to have residual WDTC by either histology (4 patients), a positive post-RAI therapy WBS (2 patients), neck or chest CT (3 patients) and ultrasound (3 patients) (Table 2). Our observations add further support to the efficacy of TSH stimulated Tg as a screening test for previously treated stage II-IV WDTC patients who have an undetectable serum Tg on T_4 therapy.

One patient was documented to have Stage IV metastatic recurrent disease without a detectable increase in serum Tg despite an absence of Tg-antibody interference and a significant rise in TSH (74.8 mIU/l). This patient was a 72-yr-old female, with documented locally invasive multifocal Stage III tall-cell variant of papillary cancer. The occurrence of metastatic papillary thyroid cancer without an increase in a TSH-stimulated serum thyroglobulin has been previously reported (21-23). Accordingly, Stage I-IV WDTC patients with undetectable stimulated serum Tg results should also have routine neck US and computed tomography (CT) studies performed to exclude unsuspected residual thyroid carcinoma. Nevertheless, follow-up on this single patient initially considered to have a false negative result on the 3-week T_4 withdrawal test has been subsequently shown to have metastatic lung disease and pleural effusion secondary to a non-thyroidal adenocarcinoma. The absence of any evidence of false positives or negatives has precluded the calculation of sensitivity, specificity, positive and negative predictive values.

We observed that withdrawal from T_4 therapy for 3 weeks was sufficient to induce a significant increase of serum TSH (level ≥25 mIU/l) in 83% of the study cohort (Fig. 2) and identified 3 possible TSH/Tg responses (Table 3). Although many authors consider TSH levels ranging from 25 to 30 mIU/l as the minimum for either a diagnostic WBS or RAI therapy (2, 5, 18, 24), lower levels of TSH may be adequate for inducing detectable levels of serum Tg. Previous studies reported that serum TSH levels of as low as 2.2-4.5 mIU/l (4, 25) stimulated serum Tg to detectable levels. Similar findings were noted in the current study in which 3 patients with TSH < 25 mIU/l (range 3-24 mIU/l) exhibited a detectable rise in serum Tg 3 weeks after T_4 withdrawal (Table 3). Based upon the sensitivity of our Tg assay and the reports of others (4, 25), we recommend a cut-off value of 2 µg/l or greater as a positive Tg result. Since a previous study using a 4-6-week T_4 withdrawal interval observed that WDTC patients with serum Tg levels of less than 3 µg/l rarely had a recurrence, while those with Tg levels greater than 5 µg/l were more likely to have significant residual WDTC (4), we suspect that patients with Tg levels ≥2 µg/l detected following a shorter 3-week T_4 withdrawal do have a significant risk for recurrent/residual disease. Three treated WDTC patients in the current study had a TSH stimulated Tg result of 1 µg/l. In accordance with the recommendation of other authors (26), detailed follow-up studies have been performed on these 3 subjects, but have failed to reveal any evidence to date of residual WDTC.

It has been well documented that withdrawal from T_4 therapy for 4-6 weeks or T_3 for 2 weeks induces severe symptomatic hypothyroidism as well as a very marked impact on quality of life and work attendance (2, 11, 12). There have also been several reports that

Table 3 - *Summary of 3 possible serum Tg/TSH responses to the 3-week T_4 withdrawal.*

	Diagnosis	% of Study Cohort
1. TSH≥25 mIU/L, Tg undetectable (<2 µg/l) → considered disease free, resume THST	Negative	75%
2. Tg detectable (≥2 µg/l) → selected for investigation & treatment	Positive	10%
3. Tg undetectable but TSH<25 mIU/l → consider for rhTSH while on THST or longer T_4 withdrawal interval to exclude residual/recurrent WDTC	Indeterminate	15%

have established the morbidity, sensitivity, specificity and predictive value of a diagnostic WBS and serum Tg testing on treated WDTC patients who had undergone such thyroid hormone withdrawal protocols as a method for stimulating endogenous TSH (5, 6). Based upon these aforementioned considerations, the inclusion in our study design of a longer hormone-withdrawal protocol on our low-risk WDTC cohort for the purposes of obtaining WBS and Tg comparisons to the utility of a stimulated-Tg (without WBS) screening test after only a 3-week T_4 withdrawal interval was deemed unjustified.

Although significant changes were observed in 6 out of 8 categories in the quality of life questionnaire administered in our study, these effects appeared to be less pronounced and of shorter duration than after a 6-week withdrawal from T_4 therapy (11, 12). Thus, compared to the previously mentioned protocols, we have observed that a 3-week withdrawal from T_4 therapy had minimal adverse effects on quality of life and health-related employment leave. To our knowledge, there are no other reports in the literature that have quantified the symptomatology associated with the other withdrawal protocols. In addition, any symptoms that were noted at clinical examination during our study were generally well tolerated. In the case of the General Health and Bodily Pain categories, there was no statistical difference between the pre-withdrawal, withdrawal and resumption of T_4 therapy stages (p=0.14) (Fig. 3). The regimen was tolerated by the majority of patients and virtually no health-related loss of employment was documented. Any QOL deficits rapidly returned to pre-withdrawal levels following resumption of T_4/T_3 therapy.

Recombinant human TSH (rhTSH), a synthetic source of TSH, is an alternative method for stimulating serum Tg. This method is attractive because of its ability to achieve high TSH levels (116±38 mIU/l) (27) while avoiding the signs and symptoms of hypothyroidism (2, 27, 28). However, the performance of the rhTSH diagnostic protocol requires a greater time commitment because of repeated return visits within 1 week and a cost that may not be affordable to patients without private health plans (25, 26). Since our 3-week T_4 withdrawal study identified a small subgroup of patients (27/181, 15%) who exhibited an inadequate TSH response (< 25 mIU/l) in association with negative serum Tg, we recommend that such patients be considered for either rhTSH stimulation or a 4-6 week T_4 withdrawal to exclude residual WDTC. Interestingly, serum Tg levels after TSH stimulation by T_4 withdrawal are higher than those

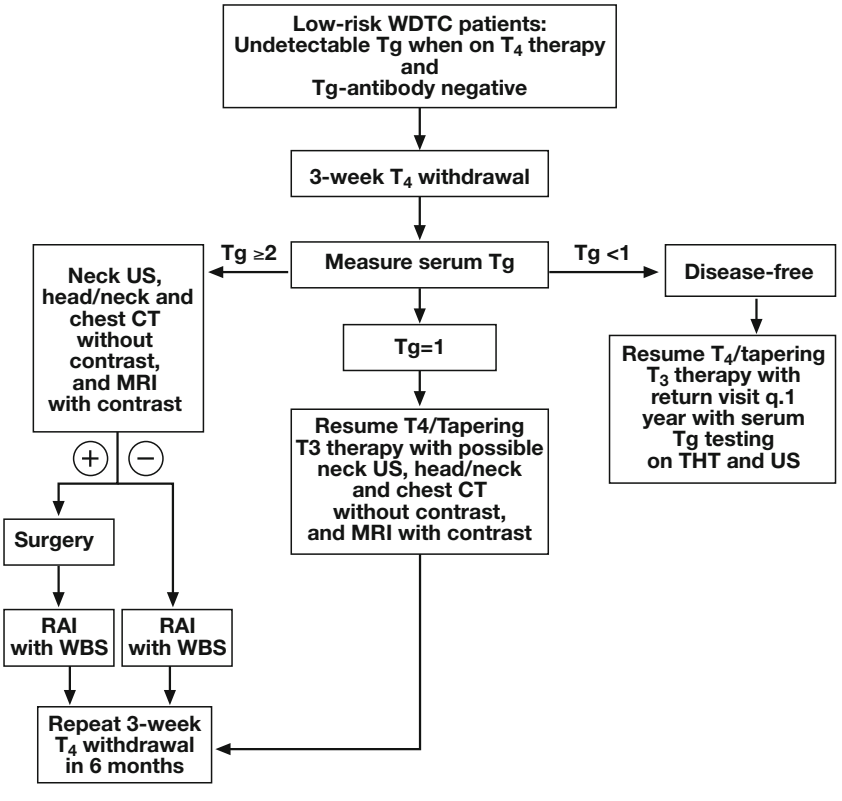

Fig. 4 - *Proposed model for the follow-up management of well-differentiated thyroid carcinoma (WDTC) patients previously treated with thyroidectomy and radioiodine therapy who have an undetectable serum Tg on T_4 suppression therapy. Imaging studies including ultrasound (US), computed tomography (CT) usually without contrast, and magnetic resonance imaging (MRI) using contrast when indicated are shown. Radioactive iodine (RAI) therapy followed by whole body scanning (WBS) is prescribed empirically as shown. Tg: thyroglobulin; THT: thyroid hormone therapy.*

achieved with rhTSH (9). This apparent discordance may be due to differing rates of Tg synthesis and clearance occurring during the hypothyroidism of T_4 withdrawal compared to the hyperthyroid metabolic state when continuing T_4 suppression therapy (9). Although 3 patients with a TSH <25 mIU/l had a positive serum Tg response despite a TSH <25 mIU/l (Table 2, patients 3, 4 and 13), we recommend that Stage II-IV patients with a negative serum Tg and a serum TSH less than 25 mIU/l be considered for either rhTSH stimulation or a more prolonged T_4 withdrawal interval to exclude residual disease.

In the past, a diagnostic WBS has been considered to be the principal diagnostic test for detecting residual/recurrent WDTC. Recently, however, several reports have indicated that a diagnostic WBS has limited utility compared to a stimulated serum Tg test in detecting residual/recurrent metastases (9, 29). The current study also documents the feasibility of detecting residual/recurrent WDTC without the routine use of a diagnostic WBS (Table 2). Accordingly, we have utilized a 3-week T_4 withdrawal TSH stimulated Tg test as a strategy (Fig. 4) for the investigation and further management of treated WDTC with an undetectable serum Tg on T_4 therapy. In this approach, patients with lesions suitable for resection underwent surgical removal, while others without detectable residual disease received empirical RAI therapy followed by a post-^{131}I therapy WBS. Those patients who have a negative post-RAI WBS and a persistently elevated Tg can be considered for future US, CT and magnetic resonance imaging (MRI) procedures.

In conclusion, we have shown that withdrawal from T_4 therapy for 3 weeks can facilitate the detection of residual/recurrent thyroid cancer in most previously treated low-risk WDTC patients by the measurement of a stimulated serum Tg without a routine diagnostic WBS. Since this screening test has a decreased and more tolerable adverse effect on quality of life and loss of work time than currently recommended thyroid hormone withdrawal protocols, we believe that it is a sufficiently sensitive, practical and cost-effective first-line screening test for excluding residual/recurrent thyroid carcinoma among the majority of low-risk WDTC patients, i.e. those who have an undetectable Tg on T_4 after a previous surgery and RAI therapy (i.e. 75% of the total cohort). At the same time, this screening test identifies two other subgroups among the remaining 25% of low-risk WDTC subjects. One subgroup (~10% of the total cohort) is identified with a positive serum Tg result that will require further investigation and probable treatment (Fig. 4). The remaining subgroup (~15% of the total cohort) has a negative serum Tg (<2µg/l) with an inadequate serum TSH response to a 3-week T_4 withdrawal challenge test. Patients in this subgroup will require either a 4-6-week T_4 withdrawal study in an attempt to increase serum TSH to values greater than 25 mIU/l or could be selected as candidates for rhTSH administration without T_4 withdrawal to avoid the quality of life consequences of severe symptomatic hypothyroidism and ensure that adequate TSH stimulation is achieved.

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