Stimulated Tg level measurements may be avoided in differentiated thyroid carcinoma patients who have undetectable basal Tg levels

Ebuzer Kalender¹, Umut Elboga^{1*}, Y.Zeki Celen¹, Hasan Deniz Demir¹, Ertan Sahin², Seyhan Karaçavuş³, Mustafa Basibuyuk¹ and Mustafa Yilmaz¹

*Correspondence: umutelboga@hotmail.com

¹University of Gaziantep, School of Medicine, Department of Nuclear Medicine, Gaziantep, Turkey.

²University of Namik Kemal, School of Medicine, Department of Nuclear Medicine, Tekirdag, Turkey.

³University of Bozok, School of Medicine, Department of Nuclear Medicine, Yozgat, Turkey.

Abstract

Background: The aim of this retrospective study is to evaluate the diagnostic value of undetectable basal thyroglobulin (Tg) levels measured 6 months after ablative ¹³¹I treatment (AIT) in patients with differentiated thyroid carcinoma (DTC).

Methods: The study included 159 patients (140 women, 19 men with mean age 43.4±15.6) who had undetectable basal Tg levels (<0.2 ng/ml) and negative anti-Tg antibodies, 6 months after AIT. Histologic examination was papillary thyroid carcinoma in 151 patients and follicular thyroid carcinoma in 8 patients. To control the AIT efficacy, diagnostic whole body scan (DWBS) was planned 6 months after AIT. Before DWBS, basal and stimulated Tg levels were measured and compared. Then all patients underwent DWBS.

Results: All patients (with undetectable basal Tg level) had a stimulated Tg level under 2 ng/ml. Stimulated Tg levels were undetectable (<0.2 ng/ml) in 142 (89.3%) patients and 0.58±0.26 ng/ml (range 0.3-1.3 ng/ml) in 17 (10.7%) patients. The control DWBS, 6 months after thyroid ablation, was negative in 151 (95%) patients and was positive for minimal residual uptake on the thyroid bed in 8 (5%) patients. Stimulated Tg levels of patients with residual thyroid bed uptake on control DWBS, were undetectable (<0.2 ng/ml) in 4 patients and 0.8±0.19 ng/ml (range 0.3-1.3 ng/ml) in 4 patients.

Conclusion: Our data suggest that stimulated Tg level measurements may be avoided in DTC patients with undetectable basal Tg levels. Thus, unnecessary Tg stimulation with rhTSH or endogen TSH, diagnostic procedures (DWBS) and radiation exposure can be reduced.

Keywords: Differentiated thyroid carcinoma, follow-up, thyroglobulin, diagnostic whole-body scan

Introduction

The large majority of patients with thyroid carcinoma have well differentiated tumors that are completely cured by surgery and thyroid ablation with radioiodine [1]. Lifelong follow-up of patients with differentiated thyroid carcinoma (DTC) is important because recurrences may occur over time [2-4]. Thyroglobulin (Tg) measurements are the main tool in the management and follow-up of patients with DTC [5,6]. Serum Tg can be measured during thyroid hormone suppression therapy (basal Tg) or thyroid-stimulating hormone (TSH) stimulation with recombinant human TSH (rhTSH) or endogenously (stimulated Tg). Stimulated Tg measurement is more sensitive than the basal Tg measurement [7]. But the basal Tg measurement is important component of the follow-up. Basal Tg measurement using high-sensitive assays proved to be effective [8].

The aim of this retrospective study is to evaluate the diagnostic value of undetectable basal Tg levels measured 6 months after ablative ¹³¹I treatment (AIT) in patients with DTC.

Methods

One hundred and fifty-nine patients (140 women, 19 men

with mean age 43.4±15.6 years) who had undetectable basal Tg levels (<0.2) and negative anti-Tg antibodies, 6 months after postsurgical radioablation treatment between January 2008 and January 2013 were selected for this retrospective study. Histologic examination revealed papillary thyroid carcinomas in 151 patients and follicular thyroid carcinomas in 8 patients.

Patients were treated by a total or near-total thyroidectomy followed by AIT, initially. Within a few months after surgery, patients were given 75-100 mCi ¹³¹I for remnant ablation after at least 3 week withdrawal of hormone therapy. A posttreatment ¹³¹I whole body scan (PWBS) was performed 5-10 days after AIT to all patients. To control the AIT efficacy, diagnostic whole body scan (DWBS) was planned 6 months after AIT. Before DWBS basal Tg levels and anti-Tg antibody levels were measured. Then patients discontinued taking thyroxine and followed a low-iodine diet during 3 weeks. Just before DWBS, stimulated Tg and anti-Tg antibody levels were measured when TSH>30 IU/ml. Tg levels were measured using immunoradiometric analyzer that uses paramagnetic microparticles and chemiluminescent detection technology with a lower detection limit of 0.2 ng/ml. After TSH stimulation, 5 mCi (185 MBq)

Table 1. Demographic and clinical features of all patients.

Age	43.4±15.6
Gender (M/F)	19/140
Pathology	
PTC	151
FTC	8
Basal Tg (in all p., ng/ml)	<0.2
Stimulated Tg (ng/ml)	
in 142 p. (89.3%)	<0.2
in 17 p. (10.7 %)	0.58±0.26
DWBS	
positive	8
negative	151

PTC: Papillary thyroid carcinoma

FTC: Follicular thyroid carcinoma

Tg: Thyroglobulin

p: patient

DWBS: Diagnostic whole-body scan

¹³¹I was given orally to the patients and 2-3 days later, DWBS was performed to all patients.

During the follow-up, basal Tg and anti-Tg antibody levels were also measured in three month intervals. Statistical analysis and the calculations were performed using SPSS 11.0 for Windows. Differences were considered statistically significant at P<0.05.

Results and discussion

After surgery, all patients underwent thyroid ablation with ¹³¹I, at doses ranging from 75–100 mCi, followed by PWBS. Thyroid remnants were present on PWBS in all patients and there was no foci of pathologic radioiodine uptake outside the thyroid bed. Six months later, all patients who had undetectable basal Tg levels, underwent the control DWBS and serum Tg measurement in the hypothyroid state. At this time, all patients had a stimulated Tg level under 2 ng/ml. Stimulated Tg levels were undetectable (<0.2 ng/ml) in 142 (89.3%) patients and 0.58±0.26 ng/ml (range 0.3-1.3 ng/ml) in 17 (10.7%) patients. The control DWBS, 6 months after thyroid ablation, was negative in 151 (95%) patients and was positive for minimal residual uptake on the thyroid bed in 8 (5%) patients. There was no statistically significant difference between patients that stimulated Tg levels were undetectable (<0.2 ng/ml) and detectable (range 0.3-1.3 ng/ml) in the control DWBS findings (P=0.32). No patient had scintigraphic or clinical evidence of local or distant metastases. Demographic and clinical features of patients are given in (Table 1).

Stimulated Tg levels of patients with residual thyroid bed uptake on control DWBS were undetectable (<0.2 ng/ml) in 4 patients and 0.8±0.19 ng/ml (range 0.3-1.3 ng/ml) in the remaining 4 patients. The between of the patients that have undetectable and detectable Tg levels were not statistically significant for thyroid bed uptake on control DWBS.

Some imaging methods and laboratory tests are used on the follow-up of patients with DTC. Diagnostic whole body scan is

one of the imaging methods. six-twelve months after thyroid ablation in the hypothyroid state, negative DWBS results with undetectable Tg levels are usually associated with complete remission [9]. In general, DWBS has a little help on the follow up DTC patients. Many studies have shown that the DWBS is almost no informative in patients who have undetectable stimulated Tg and negative anti-Tg antibodies [10-12]. On the other hand PWBS may detect new foci of tumor not seen on DWBS in up to 50% of patients [13,14].

¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) can be useful in patients who have positive Tg level and negative radioiodine scan. An elevated serum Tg level (>10 ng/ml) with negative PWBS results is the main indication for ¹⁸F-FDG PET [15,16]. ¹⁸F-FDG PET also provides prognostic information. ¹⁸F-FDG-avid metastatic DTC lesions are usually resistant to ¹³¹I treatment [17].

Neck ultrasonography plays an important role in the follow-up of patients with DTC. Stimulated Tg measurements and neck ultrasonography (US) provide the best sensitive and specific combination for identifying DTC patients with persistent or recurrent disease [1,18].

Serum Tg measurement is the most important component of follow-up. Tg is a thyroid-specific protein which is the precursor element of thyroid hormone biosynthesis [19]. It is secreted from either normal thyroid tissue or functioning malignant cells of DTC. Because of the thyroid is the only source of Tg, a rise in its level in patients after thyroidectomy and radioiodine ablation indicates the recurrence of DTC. Sensitivity of Tg is limited in the presence of anti-Tg antibodies and serum heterophile antibodies (HAB). In the presence of anti-Tg antibodies, levels of Tg can be mistakenly low. Anti-Tg antibodies are detected in approximately 20% of patients with DTC, compared with the 10% incidence reported for the general population [20,21]. Anti-Tg antibody concentrations typically fall to undetectable levels in a median of 3 years after a successful treatment [22]. HAB leads to a false elevation in serum Tg levels. Preissner *et al.*, found that HAB interference caused false Tg elevations in up to 3% of their patients. HAB interference should be suspected when Tg levels do not match the clinical findings [23].

In fact, stimulated Tg measurement is more sensitive than the basal Tg measurement [7]. Basal Tg measurement using high-sensitive assays proved to be effective [8]. Serum Tg assay sensitivity has greatly improved in the last decades, lowering the analytical sensitivity from 0.8 ng/ml to 0.01 ng/ml [24,25]. By using high-sensitive Tg assays, few patients with undetectable basal Tg had a Tg response higher than 2 ng/ml to rhTSH stimulation [26,27]. Some recent studies recommend that a Tg assay with a functional sensitivity of 0.1 ng/ml may reduce the need to perform stimulated Tg measurements [2,26-32].

Smallridge *et al.*, showed that a basal Tg <0.1 ng/ml was highly predictive for a stimulated Tg <2 ng/ml, thus eliminating the necessity for use of recombinant TSH in a large number of patients [26]. Malandrino *et al.*, using an assay with a functional

sensitivity of 0.1 ng/ml, reported that only 5 (1.4%) of the 356 patients with basal Tg levels no higher than 0.15 ng/ml had stimulated Tg levels higher than 2 ng/ml and none of them had recurrences on the follow-up [31]. In contrast, 33 of 69 with a basal Tg >0.15 ng/ml had recurrences. Spencer *et al.*, found that only 0.3% of 655 patients with basal Tg <0.1 had a stimulated Tg >2 ng/ml, by using a sensitive Tg assay [32].

Conclusion

In our study, we found that 159 patients with undetectable basal Tg level, had a stimulated Tg level under 2 ng/ml and 142 (89.3%) of them had an undetectable stimulated Tg level. In conclusion our data suggest that stimulated Tg level measurements may be avoided in DTC patients with undetectable basal Tg levels. Thus, unnecessary Tg stimulation with rhTSH or endogen TSH, diagnostic procedures (DWBS) and radiation exposure can be reduced.

Competing interests

The authors declare that they have no competing interests.

Publication history

Editor: Umid Kumar Shrestha, Manipal College of Medical Sciences, Nepal.

Received: 23-Apr-2013 Revised: 30-May-2013

Accepted: 10-Jun-2013 Published: 17-Jun-2013

References

- Pacini F, Molinaro E, Castagna MG, Agate L, Elisei R, Ceccarelli C, Lippi F, Taddei D, Grasso L and Pinchera A: **Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma.** *J Clin Endocrinol Metab* 2003, **88**:3668-73. | [Article](#) | [PubMed](#)
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL and Tuttle RM: **Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer.** *Thyroid* 2009, **19**:1167-214. | [Article](#) | [PubMed](#)
- Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F, Martino E and Pinchera A: **Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine.** *World J Surg* 1994, **18**:600-4. | [Article](#) | [PubMed](#)
- Mazzaferri EL and Kloos RT: **Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer.** *J Clin Endocrinol Metab* 2001, **86**:1447-63. | [Article](#) | [PubMed](#)
- Mazzaferri EL: **NCCN thyroid carcinoma practice guidelines.** *Oncology*. 1999, **13**:391-442. | [Website](#)
- Schlumberger MJ: **Papillary and follicular thyroid carcinoma.** *N Engl J Med* 1998, **338**:297-306. | [Article](#) | [PubMed](#)
- Haugen BR, Pacini F, Reiners C, Schlumberger M, Ladenson PW, Sherman SI, Cooper DS, Graham KE, Braverman LE, Skarulis MC, Davies TF, DeGroot LJ, Mazzaferri EL, Daniels GH, Ross DS, Luster M, Samuels MH, Becker DV, Maxon HR, 3rd, Cavalieri RR, Spencer CA, McEllin K, Weintraub BD and Ridgway EC: **A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer.** *J Clin Endocrinol Metab* 1999, **84**:3877-85. | [Article](#) | [PubMed](#)
- Rosario PW, Borges MA, Fagundes TA, Franco AC and Purisch S: **Is stimulation of thyroglobulin (Tg) useful in low-risk patients with thyroid carcinoma and undetectable Tg on thyroxin and negative neck ultrasound?** *Clin Endocrinol (Oxf)* 2005, **62**:121-5. | [Article](#) | [PubMed](#)
- Schlumberger M and Baudin E: **Serum thyroglobulin determination in the follow-up of patients with differentiated thyroid carcinoma.** *Eur J Endocrinol* 1998, **138**:249-52. | [Article](#) | [PubMed](#)
- Cailleux AF, Baudin E, Travagli JP, Ricard M and Schlumberger M: **Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer?** *J Clin Endocrinol Metab* 2000, **85**:175-8. | [Article](#) | [PubMed](#)
- Huang SH, Wang PW, Huang YE, Chou FF, Liu RT, Tung SC, Chen JF, Kuo MC, Hsieh JR and Hsieh HH: **Sequential follow-up of serum thyroglobulin and whole body scan in thyroid cancer patients without initial metastasis.** *Thyroid* 2006, **16**:1273-8. | [Article](#) | [PubMed](#)
- Taylor H, Hyer S, Vini L, Pratt B, Cook G and Harmer C: **Diagnostic 131I whole body scanning after thyroidectomy and ablation for differentiated thyroid cancer.** *Eur J Endocrinol* 2004, **150**:649-53. | [Article](#) | [PubMed](#)
- Pacini F, Agate L, Elisei R, Capezzone M, Ceccarelli C, Lippi F, Molinaro E and Pinchera A: **Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic (131I) whole body scan: comparison of patients treated with high (131I) activities versus untreated patients.** *J Clin Endocrinol Metab* 2001, **86**:4092-7. | [Article](#) | [PubMed](#)
- Schlumberger M, Mancusi F, Baudin E and Pacini F: **131I therapy for elevated thyroglobulin levels.** *Thyroid* 1997, **7**:273-6. | [Article](#) | [PubMed](#)
- Lind P, Kresnik E, Kumnig G, Gallowitsch HJ, Igerc I, Matschnig S and Gomez I: **18F-FDG-PET in the follow-up of thyroid cancer.** *Acta Med Austriaca* 2003, **30**:17-21. | [Article](#) | [PubMed](#)
- Helal BO, Merlet P, Toubert ME, Franc B, Schvartz C, Gauthier-Koelesnikov H, Prigent A and Syrota A: **Clinical impact of (18)F-FDG PET in thyroid carcinoma patients with elevated thyroglobulin levels and negative (131I) scanning results after therapy.** *J Nucl Med* 2001, **42**:1464-9. | [Article](#) | [PubMed](#)
- Wang W, Larson SM, Tuttle RM, Kalaigian H, Kolbert K, Sonenberg M and Robbins RJ: **Resistance of [18f]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine.** *Thyroid* 2001, **11**:1169-75. | [Article](#) | [PubMed](#)
- Mazzaferri EL and Kloos RT: **Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation?** *J Clin Endocrinol Metab* 2002, **87**:1490-8. | [Article](#) | [PubMed](#)
- Low TH, Delbridge L, Sidhu S, Learoyd D, Robinson B, Roach P and Sywak M: **Lymph node status influences follow-up thyroglobulin levels in papillary thyroid cancer.** *Ann Surg Oncol* 2008, **15**:2827-32. | [Article](#) | [PubMed](#)
- Kim ES, Lim DJ, Baek KH, Lee JM, Kim MK, Kwon HS, Song KH, Kang MI, Cha BY, Lee KW and Son HY: **Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules.** *Thyroid* 2010, **20**:885-91. | [Article](#) | [PubMed](#)
- Spencer C, Petrovic I and Fatemi S: **Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer.** *J Clin Endocrinol Metab* 2011, **96**:1283-91. | [Article](#) | [PubMed](#)
- Grebe SK: **Thyroglobulin autoantibodies, thyroid nodules, and new insights into some old questions.** *Thyroid* 2010, **20**:841-2. | [Article](#) | [PubMed](#)
- Preissner CM, O'Kane DJ, Singh RJ, Morris JC and Grebe SK: **Phantoms in the assay tube: heterophile antibody interferences in serum thyroglobulin assays.** *J Clin Endocrinol Metab* 2003, **88**:3069-74. | [Article](#) | [PubMed](#)
- Van Herle AJ, Uller RP, Matthews NI and Brown J: **Radioimmunoassay for measurement of thyroglobulin in human serum.** *J Clin Invest* 1973, **52**:1320-7. | [Article](#) | [PubMed Abstract](#) | [PubMed Full Text](#)
- Iervasi A, Iervasi G, Bottoni A, Boni G, Annicchiarico C, Di Cecco P and Zucchelli GC: **Diagnostic performance of a new highly sensitive thyroglobulin immunoassay.** *J Endocrinol* 2004, **182**:287-94. | [Article](#) | [PubMed](#)

26. Smallridge RC, Meek SE, Morgan MA, Gates GS, Fox TP, Grebe S and Fatourechi V: **Monitoring thyroglobulin in a sensitive immunoassay has comparable sensitivity to recombinant human tsh-stimulated thyroglobulin in follow-up of thyroid cancer patients.** *J Clin Endocrinol Metab* 2007, **92**:82-7. | [Article](#) | [PubMed](#)
27. Iervasi A, Iervasi G, Ferdeghini M, Solimeo C, Bottoni A, Rossi L, Colato C and Zucchelli GC: **Clinical relevance of highly sensitive Tg assay in monitoring patients treated for differentiated thyroid cancer.** *Clin Endocrinol (Oxf)* 2007, **67**:434-41. | [Article](#) | [PubMed](#)
28. Rosario PW and Purisch S: **Does a highly sensitive thyroglobulin (Tg) assay change the clinical management of low-risk patients with thyroid cancer with Tg < 1 ng/ml determined by traditional assays?** *Clin Endocrinol (Oxf)* 2008, **68**:338-42. | [Article](#) | [PubMed](#)
29. Schlumberger M, Hitzel A, Toubert ME, Corone C, Troalen F, Schlageter MH, Claustrat F, Koscielny S, Taieb D and Toubreau M et al.: **Comparison of seven serum thyroglobulin assays in the follow-up of papillary and follicular thyroid cancer patients.** *J Clin Endocrinol Metab* 2007, **92**:2487-95. | [Article](#) | [PubMed](#)
30. Zophel K, Wunderlich G and Smith BR: **Serum thyroglobulin measurements with a high sensitivity enzyme-linked immunosorbent assay: is there a clinical benefit in patients with differentiated thyroid carcinoma?** *Thyroid* 2003, **13**:861-5. | [Article](#) | [PubMed](#)
31. Malandrino P, Latina A, Marescalco S, Spadaro A, Regalbuto C, Fulco RA, Scollo C, Vigneri R and Pellegriti G: **Risk-adapted management of differentiated thyroid cancer assessed by a sensitive measurement of basal serum thyroglobulin.** *J Clin Endocrinol Metab* 2011, **96**:1703-9. | [Article](#) | [PubMed](#)
32. Spencer C, Fatemi S, Singer P, Nicoloff J and Lopresti J: **Serum Basal thyroglobulin measured by a second-generation assay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer.** *Thyroid* 2010, **20**:587-95. | [Article](#) | [PubMed](#)

Citation:

Kalender E, Elboga U, Celen YZ, Demir HD, Sahin E, Karaçavuş S, Basibuyuk M and Yilmaz M: **Stimulated tg level measurements may be avoided in differentiated thyroid carcinoma patients who have undetectable basal tg levels.** *Internal Medicine Inside* 2013, **1**:5.
<http://dx.doi.org/10.7243/2052-6954-1-5>