BEHAVIOUR OF EARLY THYROGLOBULIN AFTER TOTAL THYROIDECTOMY FOR DIFFERENTIATED THYROID CANCER

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Abstract

Context. The objectives of treatment of thyroid carcinoma include hormonal suppression, radioiodine ablation and follow-up with serum thyroglobulin (Tg). Tg levels should not be measured before six weeks post-thyroidectomy.

Objective. To describe the behaviour of early postoperative Tg in patients who underwent total thyroidectomy and its ability to predict the serum Tg levels after suppression.

Design. This is a retrospective cohort study.

Subjects and methods. Adult patients who underwent total thyroidectomy with at least two postoperative measurements of serum Tg, negative TgAb and concomitant serum TSH values were included. Tg, TgAb and TSH level measurements were completed two weeks postoperatively and during the follow-up period.

Results. Twenty-nine patients fulfilled all criteria. The median serum Tg level at two weeks after surgery was 3.8 ug/L (0.3 -300) with a serum TSH level of 69.9 mU/L; 11-227. At the two-week measurement, 16 (55%) patients had serum Tg levels lower than 5 ug/L and 4 patients had levels between 5-10 µg/L.

Conclusions. Postoperative early serum Tg could be an alternative to values measured six months after surgery and could be used as a predictive tool to make earlier therapeutic decisions.

Key words: well differentiated thyroid carcinoma, thyroglobulin, follow-up, radioiodine ablation.

INTRODUCTION

Well-differentiated thyroid carcinoma (WDTC) is the most frequent endocrine neoplasia, with a high rate of cure and low metastatic potential. Five per cent of cases have a more aggressive behaviour with local and regional recurrence at the diagnosis or during the first 5 years after primary treatment (1). Disease recurrence happens in 3-20% of patients and 5-10% of patients exhibit systemic metastases according to basal

risk groups.

In addition to oncologic surgery, the objectives of treatment for WDTC include hormonal support or suppression with levothyroxine (LT4) as well as radioiodine ablation (RAI) in selected cases and follow-up with serum thyroglobulin (Tg) (2).

Tg is a glycoprotein synthesized by thyroid follicular cells by hepatic metabolism and with a half-life of 30 hours (3). Most Tg is secreted to the thyroid follicle, but when thyroid hormones are synthesized by iodination of Tg and secreted following proteolysis under control of thyroid-stimulating hormone (TSH), some intact molecules of Tg are secreted to serum, which increases circulating levels of Tg. These levels depend on the size of thyroid tissue, liver function and laboratory techniques used for measurement (4). Therefore, the only source of Tg is thyroid tissue, and the quantity of serum Tg depends on thyroid damage (biopsy, inflammation) and stimulation of the TSH receptor. Serum Tg has an essential role during WDTC follow-up after total thyroidectomy and RAI when thyroglobulin antibodies (TgAbs) are negative. This allows for the identification of patients with residual tissues and avoids other unnecessary testing for those without recurrence with a high sensitivity and specificity (5). Sensitivity is higher when TSH levels are greater, which is achieved by rhTSH stimulation or LT4 withdrawal (6). Undetectable serum Tg levels associated to undetectable TgAbs and a normal neck ultrasonography are highly predictive of the absence of WDTC, but patients with elevated or increased basal levels of Tg require investigation for an occult thyroid tumor (7).

According to American Thyroid Association (ATA) guidelines, serum Tg levels should not be measured before six weeks post-thyroidectomy because the clearance time is insufficient to represent the basal state and Tg levels should be measured during the follow-up period once or twice a year (2, 8).

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As a high TSH level offers a better sensitivity for the measurement of serum Tg, some authors even suggest to measure it after LT4 withdrawal or rhTSH stimulation (6). However, the first strategy produces an iatrogenic hypothyroidism with its related symptoms and the second is associated with higher costs (9, 10). An alternative to these strategies could be to measure serum Tg two weeks after surgery in the early postoperative period when Tg clearance has been achieved, hormonal support with T4 has not yet been initiated, and the patient may be exhibiting the first symptoms of hypothyroidism, which can be masked by symptoms related to the surgical injury. This alternative could avoid the subsequent withdrawal of LT4 and hypothyroidism symptoms or rhTSH stimulation and higher costs.

The aim of this study was to describe the behaviour of early postoperative Tg in patients with WDTC who underwent total thyroidectomy and its ability to predict the serum Tg levels after LT4 suppression.

MATERIAL AND METHODS

This is a descriptive retrospective study of prospective data collection. The study was approved by the research committee of Hospital Pablo Tobón Uribe, Medellín, Colombia. All clinical charts of adult patients who underwent total thyroidectomy with or without neck dissection for WDTC between 2012 and 2014 were reviewed. Inclusion criteria were age greater than 16 years, histologic confirmation of papillary or follicular thyroid cancer with at least two postoperative measurements of serum Tg, negative TgAb assessment and concomitant serum TSH values. TSH and FT4 were measured by chemoluminescent immunoassay (ref 0.35-4.9 mUI/mL and 0.70-1.48 ng/mL, respectively). Tg and TgAb was measured by electro-chemiluminescence immunoassay. Sensitivity for Tg was <0.04 ng/mL and value <100 IU/mL for TgAb is considered negative.

The protocol comprised surgery (thyroidectomy with or without neck dissection) without immediate LT4 support. After two weeks, at the first postoperative control and with the confirmation of malignancy, serum Tg, TgAb and TSH level measurements were completed and LT4 support was initiated at 1.5-2 mcg/Kg/dose after blood collection. Then, at 2-6 months following LT4 support, new measurements of serum Tg, TgAb, TSH and free T4 were completed according to clinical criteria. The follow-up was completed according to

ATA guidelines, and the early laboratory results were not used to make any clinical or therapeutic decisions. Data recording was made using a predesigned form and included demographic data and clinical and laboratory variables. Continuous variables are shown as the median and range (mean $\pm$ sd) for those with a non-normal distribution. Categorical variables are shown as percentages. To assess normal distribution we used the Shapiro-Wilks test. We used the Kruskal-Wallis test to compare early and late serum Tg levels.

RESULTS

We recruited 29 patients who fulfilled all criteria. The mean age was 44.7 ± 15.6 years (median 46, range 18-78), and 27(93%) patients were women. Twenty-seven (93%) patients were submitted to total thyroidectomy and 18 (62%) to neck dissection (Table 1).

The mean tumor diameter was 16.9 ± 8.4 mm (18; 4-38). The histopathologic characteristics of the patient tumors are shown in Tables 2 and 3. Twenty-one (72%) patients received RAI with I¹³¹ in the six months after surgery. All patients had a negative assay for TgAb (mean 32.5 UI/mL, normal value <100).

Tg and TSH had a non-normal distribution. The median serum Tg level at two weeks after surgery was 3.85 μ g/L (0.3 - 300) (mean 28.9 ± 76.7) with a

Table 1. Type of neck dissection

Procedure	Number (%)
Central bilateral neck dissection	8 (44)
Central bilateral + modified lateral neck dissection	4 (22)
Central unilateral	4 (22)
Central unilateral + modified lateral neck dissection	2 (12)

Table 2. Histopathologic tumor characteristics

Variable	Number (%)
Papillary type	27 (93)
Follicular type	2 (7)
Extra thyroid invasion	9 (31)
Lymphovascular invasion	4 (14)
Extracapsular lymph node invasion	4 (14)
Multicentricity	8 (28)

Table 3. pTNM stage of patients with well differentiated thyroid cancer

	N0	N1	Nx	Total
T1	3	6	6	15
T2	1	3	2	6
T3	0	6	2	8
Total	4	15	12	29

concomitant median serum TSH level of 69.9 mU/L; 11-227 (mean 80.4 ± 50.1). Two patients in this group showed serum Tg levels higher than 100 µg/L and had a diagnosis of metastatic disease. The median serum Tg level at follow-up was 0.35 µg/L (0-30.8) (mean 3.5 ± 7.8) with a concomitant median serum TSH level of 0.3 mU/L (0-95) (mean 8.3 ± 20.7). Three patients have TSH higher than normal values. The mean time between laboratory measurements was 206.6 ± 166.8 days (143; 45-721). All of the late Tg measurements were made before the RAI treatment. There was a statistically significant decrease in the serum Tg levels from two weeks postoperative to follow-up levels. ($p=0.0006$).

Regarding the two-weeks postoperative serum Tg levels, 16 (55%) patients had levels lower than 5 µg/L; 4 patients had levels between 5-10 µg/L and 9 patients had levels >10 µg/L. In the follow-up with suppressed Tg, 26 (90%) had levels lower than 5 µg/L. Twenty-seven patients had a decrease in serum Tg levels. We only identified an increase in serum Tg levels in 2 patients, one from 2 µg/L to 3 µg/L and the other from 1.89 µg/L to 2 µg/L, but these increases were not clinically significant (Fig. 1). At two weeks after surgery, all patients were considered treated with a curative attempt. At the last assessment, 27 patients were free of disease, and 2 had metastatic disease. The overall follow-up time was 404.6 ± 207 days (348; 118-731).

DISCUSSION

Thyroid cancer is the most frequent endocrine neoplasia with a world annual incidence of 11.8

Figure 1. Behavior of individual serum Tg levels over time.
1era TG: First Tg. 2da TG: Second Tg.

x 100.000 inhabitants (11) and the most common histology is papillary. Treatment of WDTC is based on thyroidectomy and RAI when necessary. During follow-up, imaging with ultrasonography and Tg, TgAb and TSH serum levels measurement are the cornerstone (12). Tg measurement helps to monitor patients in order to detect recurrence because it is produced by normal and most malignant thyroid cells. Many studies have evaluated the prognostic value of serum Tg measurements in thyroid cancer follow-up (13, 14). A high serum Tg level in the postoperative period is highly suspicious of thyroid remnant, residual tumor or recurrence, but cut points to differentiate each of these stages depends on many variables such as the size of remaining thyroid tissue, type of surgery, TSH levels and even laboratory assays (8). In the absence of TgAb interference, serum Tg is highly sensitive and specific to detect thyroid cancer recurrence, even if the measurement is performed under LT4 withdrawal or rhTSH stimulation. However, small quantities of tumor tissue cannot be detected in some cases when serum Tg is measured under LT4 suppression (2), but some studies have demonstrated that serum Tg levels can decrease even after time periods as long as 18-24 months after treatment (15, 16).

The serum values of stimulated Tg with TSH values higher than 30 µg/L is a good predictor of disease remission and could be used to stratify the risk after surgery. Gonzalez *et al.* (5) demonstrated in a cohort of 133 patients in whom serum values of stimulated Tg after surgery and before RAI ablation (virgin of postoperative treatment) were lower than 8.55 µg/L that 95% of patients were disease free at 18-24 months. Rosario *et al.* (17), in a study with 237 low-risk patients, defined a cut point of 10 µg/L associated with normal ultrasound as good predictor of the absence of a tumor with a negative predictive value of 100%. In a meta-analysis of 3947 patients, Webb *et al.* (18) defined a preablative stimulated Tg value lower than 10 µg/L as the cut point with the highest sensitivity and specificity to predict the absence of biochemical or structural evidence of disease. Therefore, the initial Tg value could be an early marker that allows for the identification of low risk patients without disease and high risk patients with metastatic disease. These studies measured serum Tg some months after surgery but previous to the ablation, indicating that the patient was free of any complementary treatment, as in our protocol.

According to ATA guidelines, serum Tg should not be measured before six weeks after thyroidectomy

and once or twice a year during follow-up. (2) This recommendation concerning the time after surgery is based on the results of the LoGerfo *et al.* (19) Hoevar *et al.* (4) and Giovanella *et al.* (20) regarding the behaviour of serum Tg. In 1978, Gerfo *et al.* studied 8 patients with malignancy who underwent total thyroidectomy and concluded that the average half-life of serum Tg was 14 (8-22) hours and suggested that 4 weeks will be the ideal time to allow the clearance of serum Tg. In 1997, Hoevar *et al.* (4) studied eleven patients with metastatic disease, two who had malignancies and underwent total thyroidectomy, and nine who underwent partial thyroidectomy. In his study he determined a half-life of 62.4 hours and concluded that a period longer than 25 days would be necessary to clear serum Tg to levels lower than 10 mcg/L. The conclusions of these studies could be biased by the type of surgery, the inclusion of an outlier with a level of serum Tg of almost 6000 ng/mL and the type of assay used at this time. Giovanella *et al.* (20) included 96 patients with thyroid cancer who underwent total thyroidectomy and determined a half-life of 28-30 hours for non-metastatic patients and 35-41 hours for metastatic patients. If we accept a half-life of 30 hours and use the formula proposed by these authors, at 360 hours (two weeks) serum Tg levels will be approximately 0, which indicates that measurements made at two weeks are as reliable as measurements made at later times.

In our study, 58% of patients had serum Tg levels lower than 5 µg/L with a median of 3.5 µg/L and median of TSH of 64 mUI/L at two postoperative weeks. At this time, all patients have surgically treated with a curative attempt and were clinically free of disease according to stage and ATA risk classification. Similar to patients included in previous studies (5, 17, 18), our patients had high levels of TSH, previous to RAI ablation and free of treatment in a time period that offers a reliable measurement when the Tg levels are informative and could help to make decisions.

According to the ATA, low risk patients who require RAI ablation and have undetectable serum Tg levels, negative TgAb and a normal neck ultrasound under LT4 withdrawal do not require continuous serum marker measurement (2). Some studies even suggest that RAI ablation can be selected according to preablative serum Tg levels, avoiding its use in patients with low serum Tg levels (21). Therefore, if possible for low risk patients with low early serum Tg levels, the ablation can be avoided.

What are the advantages of this alternative? First, patients experience a myriad of symptoms in the

postoperative period due to the metabolic response to surgical trauma that can overlap those produced by postoperative hypothyroidism. Therefore, the effects of 3-4 weeks of LT4 withdrawal on quality of life that is more evident in euthyroid patients who withdraw the LT4, will pass unnoticed with a better tolerance and in a short period of time. Second, the time to make a decision about ablation will be shortened. If the two week postoperative serum Tg level is already lower than 2 µg/L, ablation can be avoided. On the contrary, unexpectedly high levels of serum Tg that are suspicious of metastasis, as occurred with two patients, will mandate determination of the metastatic foci and favor an early systemic treatment with higher doses of RAI. Third, if early serum Tg levels are low, it will offer the possibility to extend the time for the new blood tests or to avoid LT4 withdrawal to measure Tg levels. Although rhTSH has been suggested as an alternative for LT4 withdrawal with improvements in quality of life due to the short time period of induced hypothyroidism, it has an important impact on costs (9, 10). This alternative will also decrease the number of patients who require this intervention.

This study compared two situations that commonly are considered non comparable: an early stimulated Tg with a late suppressed Tg. However, in clinical settings, this is what really occurs with low-risk patients. After a first measurement of a stimulated Tg made more than six weeks after surgery under LT4 withdrawal or rTSH stimulation, later measurements of Tg are made under suppression. This situation is going to be even more common after recent recommendations of ATA guidelines (22). Even more, all late Tg measurements were made before the RAI therapy, which avoids the effect that this therapy could produce on Tg levels.

Nonetheless, this study has some weaknesses that should be noted. First, the number of patients is small. It is necessary to confirm these results in a greater cohort. Second, the follow-up time is short. As has already been described, thyroid cancer has a long latency period and requires a longer follow-up period to guarantee that our results are reliable in the long term. Third, laboratory assays are a determinant factor in the measurement of Tg levels. As we could not standardize the type of assay used, these results could be over or underestimated in comparison with other assays and studies.

In conclusion, this study suggests that postoperative serum Tg measured at two weeks could be an alternative to predict Tg values measured at six

months after surgery and could be a tool to make earlier therapeutic decisions without affecting quality of life or increasing costs.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

References

- Kim TY, Kim WG, Kim WB, Shong YK. Current status and future perspectives in differentiated thyroid cancer. *Endocrinol Metab (Seoul)* 2014;29(3):217-225.
- American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19(11):1167-1214.
- Cody V. Thyroglobulin and thyroid hormone synthesis. *Endocr Res* 1984;10(1):73-88.
- Hocevar M, Auersperg M, Stanovnik L. The dynamics of serum thyroglobulin elimination from the body after thyroid surgery. *Eur J Surg Oncol* 1997;23(3):208-210.
- Gonzalez C, Aulinas A, Colom C, Tundidor D, Mendoza L, Corcoy R, Mato E, Alcantara V, Urgell Rull E, de Leiva A. Thyroglobulin as early prognostic marker to predict remission at 18-24 months in differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* 2014;80(2):301-306.
- Eustatia-Rutten CF, Smit JW, Romijn JA, van der Kleij-Corssmit EP, Pereira AM, Stokkel MP, Kievit J. Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma, a structured meta-analysis. *Clin Endocrinol (Oxf)* 2004;61(1):61-74.
- Evans C, Tennant S, Perros P. Thyroglobulin in differentiated thyroid cancer. *Clin Chim Acta* 2015;444:310-317.
- Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR, British Thyroid A. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)* 2014;81 Suppl 1:1-122.
- Nygaard B, Bastholt L, Bennedbaek FN, Klausen TW, Bentzen J. A placebo-controlled, blinded and randomised study on the effects of recombinant human thyrotropin on quality of life in the treatment of thyroid cancer. *Eur Thyroid J* 2013;2(3):195-202.
- Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. *Thyroid* 2010;20(2):173-179.
- Vigneri R, Malandrino P, Vigneri P. The changing epidemiology of thyroid cancer: why is incidence increasing? *Curr Opin Oncol* 2015;27(1):1-7.
- Tuttle RM. Risk-adapted management of thyroid cancer. *Endocr Pract* 2008;14(6):764-774.
- Heemstra KA, Liu YY, Stokkel M, Kievit J, Corssmit E, Pereira AM, Romijn JA, Smit JW. Serum thyroglobulin concentrations predict disease-free remission and death in differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* 2007;66(1):58-64.
- Giovanella L, Maffioli M, Ceriani L, De Palma D, Spriano G. Unstimulated high sensitive thyroglobulin measurement predicts outcome of differentiated thyroid carcinoma. *Clin Chem Lab Med* 2009;47(8):1001-1004.
- Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, Meringolo D, Ferdeghini M, Tumino S, Lamartina L, Paciaroni A, Massa M, Giacomelli L, Ronga G, Filetti S, Group PTCS. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? *J Clin Endocrinol Metab* 2012;97(8):2748-2753.
- Alzahrani AS, Mohamed G, Al Shammari A, Aldasouqi S, Abdal Salam S, Shoukri M. Long-term course and predictive factors of elevated serum thyroglobulin and negative diagnostic radioiodine whole body scan in differentiated thyroid cancer. *J Endocrinol Invest* 2005;28(6):540-546.
- Rosario PW, Xavier AC, Calsolari MR. Value of postoperative thyroglobulin and ultrasonography for the indication of ablation and I¹³¹ activity in patients with thyroid cancer and low risk of recurrence. *Thyroid* 2011;21(1):49-53.
- Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, Burch HB. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. *J Clin Endocrinol Metab* 2012;97(8):2754-2763.
- Gerfo PL, Colacchio T, Colacchio D, Feind C. Serum clearance rates of immunologically reactive thyroglobulin. *Cancer* 1978;42(1):164-166.
- Giovanella L, Ceriani L, Maffioli M. Postsurgery serum thyroglobulin disappearance kinetic in patients with differentiated thyroid carcinoma. *Head Neck* 2010;32(5):568-571.
- Nascimento C, Borget I, Al Ghuzlan A, Deandreis D, Chami L, Travagli JP, Hartl D, Lumbroso J, Chougnet C, Lacroix L, Baudin E, Schlumberger M, Leboulleux S. Persistent disease and recurrence in differentiated thyroid cancer patients with undetectable postoperative stimulated thyroglobulin level. *Endocr Relat Cancer* 2011;18(2):R29-40.
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26(1):1-133.