

Thyroglobulin value in patients surgically treated for differentiated thyroid carcinoma

Gostimir Mikač^{1,2}, Siniša Stanković¹

¹Clinical Center Banja Luka, Department of Nuclear Medicine, Banja Luka, Bosnia and Herzegovina;

²University of Banja Luka, Faculty of Medicine, Banja Luka, Bosnia and Herzegovina

SUMMARY

Introduction Thyroglobulin is composed glycoprotein, and it is synthesized by follicular cells of the thyroid gland. Treatment of differentiated thyroid carcinomas involves total thyroidectomy followed by radioiodine ablation of a potential remaining tissue. The measurement of thyroglobulin in the postoperative follow-up can serve as an indicator of tumor growth or recurrence of the disease.

Objective The aim of this paper is to examine the value of thyroglobulin in patients surgically treated for differentiated thyroid cancer who had metastases in the lymph nodes of the neck, as well as in operated on patients without any evident metastasis.

Methods Thyroglobulin values in the serum of 58 patients were analyzed. Two groups were formed. The thyroglobulin value was established with the use of IRMA-hTg (¹²⁵I) system. Normal levels of thyroglobulin were from 2 ng/ml to 65 ng/ml. For all of 58 patients, thyroglobulin was determined three times. The first, so-called pre-ablation thyroglobulin was determined immediately before the application of ¹³¹I ablation dose. The second and the third measurements were conducted six to eight months and one year, respectively, after the application of the ablation dose respectively.

Results The first group consisted of 14 patients with histologically proven metastases in the lymph nodes of the neck, while the second group consisted of 44 patients without any evident metastases. The average thyroglobulin value of pre-ablation in the patients from the first group was 43.45 ng/ml, while in the second was 7.57 ng/ml. Levene's test (with $p = 0.00$, i.e. $p < 0.05$), demonstrated a statistically significant difference. Furthermore, in both groups, there was statistically significant difference between pre-ablation and post-ablation thyroglobulin values (Student's t-test with $p < 0.05$).

Conclusion It can be concluded that the average value of thyroglobulin was significantly higher in patients with lymph node metastases in the neck. We are of the opinion that the determination of thyroglobulin, despite individual variations, may serve as a good indicator to assist in monitoring of patients surgically treated for differentiated thyroid cancer.

Keywords: thyroglobulin; total thyroidectomy; ablation; thyroid gland cancer

INTRODUCTION

Thyroglobulin (Tg), which weighs 660 kilodaltons, is a glycosylated protein. It is synthesized by follicular cells of the thyroid gland and "inserted" into the lumen of thyroid follicles. The secretion of thyroid hormones triiodothyronine (T3) and tiroxin (T4) starts with micro-pinocytosis of the iodinated thyroglobulin from the follicular lumen, and regresses into thyrocytes. Thyroglobulin has a tendency to hydrolyze under the influence of lysosomal enzymes and subsequently, by the diffusion through the basement membrane, formed molecules of T3 and T4 hormones move to the capillary network [1]. Thyroglobulin molecules can avoid hydrolysis and together with hormones, through the basement membrane, enter the blood circulation [2]. High thyroglobulin values were found both in patients with follicular adenoma and in differentiated thyroid carcinoma (DTC). The abovementioned has led to the conclusion that tumor cells of papillary or follicular cancer, presumably like a normal thyrocyte, produce and secrete thyroglobulin. The amount of thyroglobulin in the circulation can increase along with the growth of tumors, greater invasion of healthy thyroid

tissue, as well as with the emergence of metastases [3]. Nevertheless, thyroglobulin does not have a special significance in the diagnosis of thyroid cancer. High thyroglobulin value is often found in patients with diffuse goiter and patients with Graves-Basedow disease [4]. Furthermore, some patients with histologically confirmed DTC preoperatively had normal thyroglobulin values.

The first step in the DTC therapy is thyroidectomy, i.e. surgical removal of the entire thyroid tissue [5]. Complete elimination of the thyroid tissue would consequently cause the absence of thyroglobulin in the serum. Such cases are rare in practice. In most cases, we come across certain thyroglobulin values, which raises the question of quality of the declaratively performed thyroidectomy. In cases of partial thyroidectomy, such as extended lobectomy and subtotal resections, different thyroglobulin values are expected in the patients' serum. The measured thyroglobulin value can help with assessing the types of residual tissue, i.e. whether the latter is normal or tumoral [6, 7]. In order to eliminate the functionally residual thyroid tissue, a pharmacological ablation is conducted. Radioactive iodine (¹³¹I), in a capsule or liquid, is administered *per os*.

Correspondence to:

Gostimir MIKAČ
Faculty of Medicine
Save Mrkalja 22
78000 Banja Luka
Republic of Srpska
Bosnia and Herzegovina
mikac@blic.net

Most commonly, it is administered in a dose of 3.7 MBq according to the prescribed procedure [8]. In the first six months after the ablation, thyroglobulin values in the serum decline to low or undetectable values, and with an adequate hormone substitution (levothyroxine), they remain as such during regular, routine check-ups. For most authors, subsequent increase of thyroglobulin values is the most reliable sign of aggravation of the disease, that is, the appearance of local recurrence, lymph nodes metastasis or distant metastasis. Most authors believe that the post-ablation thyroglobulin is an important tumor marker for DTC [9].

In contrast to the classical prognostic factors, mathematically derived value thyroglobulin doubling time (TDT) is a more valid indicator of carcinoma recurrence. The base for the calculation of TDT consists of at least four consecutive measurements of thyroglobulin in defined time intervals [10]. Giovanella et al. [11] assert that the TDT is a reliable indicator of carcinoma recurrence even in cases when 131I-scan is negative.

In cases when thyroglobulin values remain relatively high after the ablation, it is necessary to assess possible causes. Poorly performed ablation (small dose of ¹³¹I or omissions during the procedure) may be the only cause. The resistance of postoperative residual tissue should not be neglected as the second or additional cause. Interestingly, some authors have noted weaker effects of ablation in cases where the pre-ablation thyroglobulin value was relatively higher (discriminant 10 ng/ml) [12].

OBJECTIVE

The aim of this study is to determine whether the thyroglobulin values in the serum of the patients surgically treated for differentiated thyroid carcinoma could be sufficient and accurate indicators of disease progression.

METHODS

Thyroglobulin values in the serum of 58 patients were analyzed. The thyroglobulin value was established with the usage of IRMA-hTg (¹²⁵I) system and in the range of 0 to 250 ng/ml. Normal levels of thyroglobulin were from 2 ng/ml to 65ng/ml. All patients underwent total thyroidectomy. The existence of the papillary or follicular DTC was histologically proven. Two groups were formed. The first group consisted of 14 female patients, of average age of 49 years, with papillary thyroid cancer and metastases that were detected in the lymph nodes of the neck and were classified as T(2-3)N1M0. All the patients received the ablation dose ¹³¹I of 3.7 GBq.

The second group comprised 44 patients without detected metastasis, classified as T(2-3)N0M0. There were 38 female patients with an average age of 44.5 years, and six male patients, with an average age of 41 years. In the majority of patients, that is in 43 patients, papillary carcinoma was diagnosed, and only one patient (m) had follicular

carcinoma. In accordance with the decision made by the authorized consultation team, a dose of ¹³¹I in the range of 1.5 to 3.7 GBq was administrated.

Thyroglobulin was determined three times. The first determination was conducted immediately before the administration of the ablation dose of ¹³¹I, pre-ablation thyroglobulin in conditions of high TSH level. The second determination was conducted six to eight months after the application of ¹³¹I, and the third one during the second year after the ablation. At the time of the second and third thyroglobulin determination, the patients were under the appropriate substitution therapy (levothyroxine). In the monitoring period, there were no changes in physical findings. Apart from clinical examinations, all the patients underwent neck ultrasonography, whole body scintigraphy, and in several cases thorax and neck computed tomography scan. Patients in whom the presence of high thyroglobulin-antibody titer was detected were not included in the analysis.

RESULTS

The first group consisted of 14 patients. The average pre-ablation thyroglobulin value was 43.45 ng/ml, and the individual values were in the range of 2–155 ng/ml (Table 1).

In the second measurement, the average value was 1.50 ng/ml, and the individual values ranged from 0.1 ng/ml to 7.0 ng/ml. The statistical analysis, Student's t-test ($t = 2.481$, $p = 0.035$) showed a significant difference ($p < 0.05$) between the pre-ablation and the post-ablation thyroglobulin values. The average value in the third measurement was slightly higher than the previous one, i.e. 2.13 ng/ml. The individual values ranged from 0.1 ng/ml to 4.4 ng/ml.

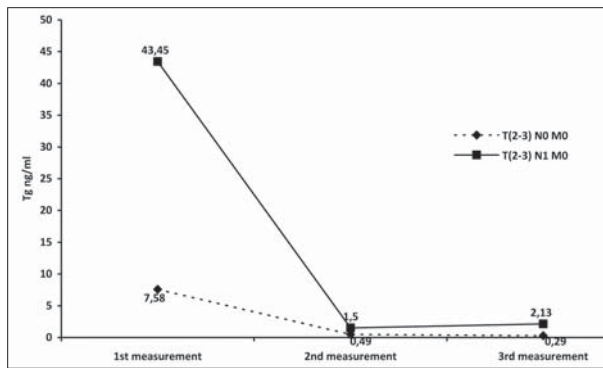
The second group comprised 44 patients. The average pre-ablation thyroglobulin value was 7.58 ng/mL, and the individual values ranged from 0.5 ng/ml to 37.0 ng/ml. In the second measurement, the average value was 0.49 ng/ml in the range of 0.1 ng/ml to 2.5 ng/ml (Table 2). There was a significant difference between the pre-ablation and post-ablation thyroglobulin values ($t = 5.473$, $p = 0.000$, i.e. $p < 0.05$). The third measurement had the average value of 0.29 ng/ml, and the individual values were from 0.1 ng/ml to 2.3 ng/ml.

Table 1. Overview of the individual and average thyroglobulin (Tg) values in the first group: T(2-3) N1 M0

Group I Tg measurement	Minimum value	Maximum value	Average value	Standard deviation
First	2.0	155.0	43.45	55.31
Second	0.1	7.0	1.50	2.17
Third	0.1	4.4	2.13	1.85

Table 2. Overview of the individual and average thyroglobulin (Tg) values in the second group: T(2-3) N0 M0

Group II Tg measurement	Minimum value	Maximum value	Average value	Standard deviation
First	0.5	37.0	7.58	8.11
Second	0.1	2.5	0.49	0.43
Third	0.1	2.3	0.29	0.39



Graph 1. Comparative overview of the average thyroglobulin (Tg) values

Basic comparison between the average pre-ablation thyroglobulin values of the first group (43.45 ng/ml) and the analog value of the second group (7.57 ng/ml) presented a clear difference (Graph 1). Statistically, group variances were significantly different (Levene's test: $F = 32.681$, $p = 0.000$, i.e. $p < 0.05$).

DISCUSSION

The importance of the thyroglobulin as a prognostic factor in patients treated for DTC is interpreted differently. Some authors believe that the pre-ablation thyroglobulin in combination with the post-ablation scintigraphy has a significant prognostic value [12]. Most authors believe that the elevated pre-ablation thyroglobulin values themselves have a significant prognostic value [13]. In this study, the average value of the pre-ablation thyroglobulin was significantly higher in the first group of patients in comparison with the second group. Unfortunately, we have no plausible explanation for the observed difference. In contrast, the range of individual values did not show such a relationship. Namely, in the first group there were four female patients who had relatively low thyroglobulin values without regard to the tumor with extrathyroidal expansion (about 2 ng/ml). On the other hand, in the second group there were three female patients with relatively high thyroglobulin values (22–30 ng/ml). A compatible attitude on normal concentration of serum thyroglobulin after the conducted thyroidectomy cannot be found in literature. Lin and associates conducted a retrospective analysis of patients who received ablation doses of ^{131}I after the thyroidectomy [13]. They decided to divide patients solely according to the ablation thyroglobulin values, and thereby the patients were divided into three groups as follows: group A ($\text{Tg} < 1 \text{ ng/mL}$), group B ($1 \text{ ng/ml} < \text{Tg} < 10 \text{ ng/ml}$), and group C ($\text{Tg} > 10 \text{ ng/ml}$). A significant difference in the incidence of recurrence was noted, i.e. in group A 4.2%, group B 23.6% and in group C even 62.9%. Hence, they generally gave a greater prognostic significance to the pre-ablation thyroglobulin. Although it is not the aim of this study, we find it useful to note that in several cases post-ablation

scintigraphy did not display focal accumulation, although it was expected to be found due to the high pre-ablation thyroglobulin values.

In the first assessment after the administration of radioactive iodine, a decrease of average thyroglobulin values in both groups was noticed. The higher thyroglobulin value in comparison with the pre-ablation thyroglobulin value was not detected at all. In all patients, the application of radioiodine therapy after the surgery was still inconsistent [14]. The above-cited results in this group support the proposition that radioiodine ablation reduces the remaining tissue. What is more, we are closer to believe that a successful ablation therapy leads to better prognosis [15,16].

In the first group, the second measurement after the application showed an increase in average values in relation to the previous measurement. Bearing in mind individual values, there was a slight increase of the thyroglobulin values in six female patients, although loco-regional changes were not observed with the use of conventional examination. Kaneko et al. [17] claim that an increase of thyroglobulin value is a sufficient indication for the use of more complicated procedures such as positron emission tomography (PET) or computed tomography (CT) in order to locate metastasis. Unexpectedly, in some patients who underwent ^{18}F -FDG-PET/CT, the results were negative [17, 18].

The second measurement in the second group showed that the average thyroglobulin value was lower in relation to the previous measurement. Individual values did not show the value higher than the previously measured one. In our case, both post-ablation thyroglobulin values were measured in terms of suppressed TSH. We believe that the post-ablation thyroglobulin values below 1 ng/ml indicate a favorable course of the disease, while in all other cases it is necessary to be alert and predict metastasis. Some authors support the notion that patients with thyroglobulin value higher than 2 ng/ml should be subjected to re-ablation, despite the fact that there are no clear, physical elements of the disease progression [19]. The thyroglobulin value would be more sensitive if it was to be determined in conditions of high TSH. Unfortunately, for patients this would mean uncomfortable exclusion of substitution for a period of two to three weeks or application of rTSH [20].

CONCLUSION

The average pre-ablation thyroglobulin value was significantly higher in the group of patients with the lymph nodes metastases of the neck when compared to the patients without metastases. The individual pre-ablation thyroglobulin values showed significant variations.

In all cases, the post-ablation thyroglobulin value was lower than the pre-ablation thyroglobulin value. In terms of adequate suppression, the post-ablation thyroglobulin monitoring has greater practical significance.

We believe that systematic thyroglobulin monitoring is needed in all patients surgically treated for differentiated thyroid carcinoma.

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Вредност тиреоглобулина код болесника оперисаних због диферентованих карцинома штитасте жлезде

Гостимир Микач^{1,2}, Сениша Станковић¹

¹Клинички центар Бања Лука, Завод за нуклеарну медицину, Бања Лука, Република Српска, Босна и Херцеговина;

²Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина

КРАТАК САДРЖАЈ

Увод Тиреоглобулин је по саставу гликопротеин, а синтетичу га фоликуларне ћелије штитасте жлезде. Лечење диферентованих тиреоидних карцинома подразумева тоталну тиреоидектомију, након које следи радиојодна аблација евентуално преосталог ткива. Мерење тиреоглобулина у постоперативном праћењу може послужити као показатељ туморског раста или рецидива болести.

Циљ рада Циљ рада јесте испитати вредности тиреоглобулина у серуму болесника оперисаних због диферентованих карцинома штитасте жлезде који су имали метастазе у лимфним нодусима врата и оперисаних болесника без евидентних метастаза.

Методe рада Анализирана је вредност тиреоглобулина у серуму 58 болесника. Формиране су две групе. Тиреоглобулин је одређиван радиоимунолошким сетовима, *IRMA-hTg* (¹²⁵I). Нормалне вредности су од 2 *ng/ml* до 65 *ng/ml*. Код свих 58 болесника тиреоглобулин је одређен три пута. Први, преаблациони тиреоглобулин је одређен непосредно пред апликацију аблационе дозе ¹³¹I. Друго одређивање

је вршено 6–8 месеци након аблације, а треће након једне године.

Резултати Прву групу чини 14 болесника са патохистолошки доказаним метастазама у лимфним нодусима врата, а другу 44 болесника без евидентних метастаза. Просечна вредност преаблационог тиреоглобулина код пацијената прве групе је била 43,45 *ng/ml*, док је у другој групи била 7,57 *ng/ml*. Левинов тест (при чему је $p = 0,00$, тј. $p < 0,05$) доказује значајну статистичку разлику. Такође, у обе групе је утврђена значајна статистичка разлика између преаблационих и постаблационих вредности тиреоглобулина (*t*-тест, при чему је $p < 0,05$).

Закључак Може се закључити да је просечна вредност тиреоглобулина значајно виша у групи болесника са метастазама у лимфним нодусима врата. Сматрамо да одређивање тиреоглобулина, упркос појединачним одступањима, може послужити као добар индикатор у праћењу болесника оперисаних због диферентованог карцинома штитасте жлезде.

Кључне речи: тиреоглобулин; тотална тиреоидектомија; аблација; карцином штитасте жлезде

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