ORIGINAL ARTICLE

STUDY OF SERUM THYROGLOBULIN IN DIFFERENTIATED THYROID CARCINOMA

Madhuri Sepuri[1], Prasadula Ashok[2], Shashiprabha K[3]

HOW TO CITE THIS ARTICLE:
Madhuri Sepuri, Prasadula Ashok, Shashiprabha K. "Study of Serum Thyroglobulin in Differentiated Thyroid Carcinoma". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 24, June 15, 2015; Page: 3616-3622.

ABSTRACT: The pattern of serum Thyroglobulin levels in thyroidectomised patients with differentiated thyroid carcinoma (DTC) was studied in retrospect. The serum thyroglobulin (Tg) levels during follow up after initial therapy, in remnant disease, association with metastasis and recurrences were evaluated. Serum thyroglobulin mean values of 4.78±0.4 ng/ml were observed in 37 subjects with successful initial therapy and no residual disease. In the group of subjects with residual disease serum thyroglobulin levels were 35.80±8.1 ng/ml. In contrast, patients with documented metastasis had serum thyroglobulin ranging from 20-1000 ng/dl with a mean of 470±369 ng/ml (n=23). Statistically significantly high values were noted in the group of subjects with metastasis at admission (n=6) and those with recurrence and metastasis (n=8) after a disease free period of 6 yrs (2-17 years) their mean values ranged from 403.85±311 ng/ml to 608±395 ng/ml respectively. In DTC with recurrence in the remnant (n=9) with a mean duration of 3.5 years following successful therapy the serum thyroglobulin levels were 159±102 ng/ml. In all the above subjects the serum thyroglobulin values profiled were over the accepted normal range of 0-10 ng/ml. This retrospective study reiterates the premise that thyroglobulin measurements provide a sensitive and pragmatic parameter in treatment and follow up of patients with differentiated thyroid carcinoma.
KEYWORDS: Serum thyroglobulin, Differentiated thyroid cancer, ^{131}I therapy.

INTRODUCTION: In a thyroidectomised patient with differentiated thyroid carcinoma, elevated serum thyroglobulin is a reflection of persistent thyroid tissue.[1] Thyroglobulin is a large glycoprotein composed of 120 tyrosyl residues, which is secreted only by thyroid gland follicular tissue and released in low concentration along with thyroid hormones into circulation. Most differentiated thyroid carcinomas (DTC) secrete thyroglobulin with exception of medullary and anaplastic thyroid carcinomas and is detected by various sensitive isotope and non-isotopic assays.[2,3] The present study evaluates the pattern of serum thyroglobulin levels and their significance relevant to the presence or absence of residual, recurrence and metastatic disease during post treatment follow up of patients with differentiated thyroid carcinoma.

MATERIAL & METHODS: This retrospective study was conducted on 68 patients, out of which 21 were male and 47 were female with mean age of 33 years (SD±12yrs); ranging from 13-71 yrs who underwent thyroid surgery and attended between January 1988 to December 2008 in the Department of Nuclear Medicine, King George Hospital, Visakhapatnam. Patients were followed for an average period of ten years from initial therapy to last visit of follow up. All the subjects had undergone total thyroidectomy, lobectomy or subtotal thyroidectomy. The histological

diagnosis was verified in all cases. Papillary carcinoma was present in 57 cases, follicular carcinoma in 8 cases and 1 case of mixed papillary follicular carcinoma. In the 68 subjects studied 44 patients had received one or more doses of therapeutic Iodine-131(^{131}I) at various times. Treatment was not given in 16 cases at any time and 6 patients had documented metastasis at the time of admission. In most cases postoperative whole body scan and neck survey with ^{131}I was performed while they were off thyroid supplementation for 4 weeks. Serum thyroglobulin was measured by Radioimmunoassay at Radiation Medicine Centre, Mumbai. All samples were analyzed in duplicate and the normal cut off range applied was

1. Intact thyroid – undetectable (UD) - 50ng/ml.
2. Thyroidectomised and on thyroxine supplementation (UD) - 9ng/ml.
3. Thyroidectomised and off thyroxine (UD) - 24.ng/ml.

No evidence of disease was defined as stimulated thyroglobulin <1ng/ml and negative WBS or normal scintigraphy. No sera of medullary thyroid carcinoma and anaplastic thyroid carcinoma were evaluated. Data was analyzed using Microsoft Excel and SSPS version 9.0.

RESULTS:

Study	Number (N)	%
Cases	68	100
Male Cases	21	30.8
Female Cases	47	69.1
Age below 45 years	12	17.6
Age above 45 years	56	82.31
Papillary Thyroid Carcinoma (PTC)	58	85.29
Follicular Thyroid Carcinoma (FTC)	10	14.7
Residual Disease	8	11.76
No Metastasis	37	54.4
Metastasis	23	33.8
Local	19	82.6
Distant	4	17.4

Table 1: Demographic features of the Study

Demographics: The demographic profile of the study given in Table 1, comprises 68 cases of thyroidectomies of which 21 were men and 56 were women, 12 were above 45 yrs and 56 were below 45 yrs. 37 subjects had undergone successful initial therapy with no residual disease and 8 had residual disease, their mean serum thyroglobulin values were 4.8±0.4 ng/ml and 35.80±8.1 ng/ml respectively. The mean for the group of subjects (n=23) with documented metastasis and statistically significantly (P value 0.005) was 470±369 ng/ml with a range of 80-1000 ng/ml. In the above group a sub group of 6 had documented metastasis at the time of admission with mean serum thyroglobulin value of 403.85±311 ng/ml. A sub group of 8 patients had recurrence

in remnant tissue after a mean period of 3.5 years with serum thyroglobulin of 159±102 ng /ml. Mean values of 608± 395 ng/ml were observed in 9 patients with evidence of tumor recurrence and metastasis after a mean disease free period of 7.3 years (2-17years). Serum thyroglobulin levels in relation to histological tumor type showed no statistically significant variation. The first year follow up thyroglobulin values measured after initial therapy were 4.1±0.89 ng/ml in PTC and 4.6±0.41 ng/ml in FTC.

Recurrence / Metastasis: Twenty five percent of cases in the study had tumor recurrence after a mean duration of 3.25 years while subjects presented with evidence of recurrence and metastasis after 7.8 years following thyroidectomy and radio ablation. Serum thyroglobulin levels in recurrence and metastasis were analyzed in 4 quarters of a five year period and presented in table 2 with their values.

Years	N	STG ng/ml (mean)	Years (mean)	%
0-5	7	375	2.85	41
6-10	8	580	7.6	47
11-15	1	121	11	5.8
16-20	1	84	17	5.8

Table 2: Serum thyroglobulin values in Recurrence & Metastasis

Highest value observed in patients with recurrence was 300 ng/ml and >1000 ng/ml in those with metastasis. Of the 8 cases of recurrence 6 were female and the reverse with 7 cases of male preponderance was observed in metastasis.

Follow up: Serial thyroglobulin values of patients after successful initial therapy and radio ablation during first and second years were analyzed. The mean values of first year were 4.78 ng/ml and second year were 0.39 ng/ml with a range of undetectable to 1 ng/ml. First year follow up of serum thyroglobulin values for patients with residual disease were 3.786±0.26 ng/ml and reflect statistically significant response to therapy ($p<0.005$)

Disease free survival period: 54% patients (n=37) were disease free after 12 months following initial therapy and 47% were at 24 months (n=32), their mean levels were 4.83±0.12 ng/ml and 1.62±0.16 ng/ml respectively with most subjects in the undetectable range at the second year follow up evaluation. Serum thyroglobulin levels measured during 1 to 20 year disease free period was tabulated in Table 3.

Therapy year	Number (N)	Serum thyroglobulin Mean SD	%
1	45	5.536±0.93	64
5	31	3.48±0.13	45
10	25	5.20±0.80	36

>10	10	3.6±0.73	18
>20	2	UD 0	3

Table 3: Serum thyroglobulin value in Disease Free Survival Period

In the evaluation of follow up data of 12 subjects during second and fifth year on thyroxine supplementation mean (Tg) values of 0.39 ngl/ml and 0.30 ng/ml were observed respectively and were statistically significant p<005. Present study serum thyroglobulin results were compared with Van herle et al[4] in Table 4.

Serum thyroglobulin status	Van Herle	Current Study
After Successful Initial Therapy Without metastasis	4.9±0.51	4.8±0.4
Metastasis & Recurrence	464±156.6	470±369

Table 4: Van Herle vs. Current study S. thyroglobulin values

Limitations of the present study: Many cases were lost to follow up after 5 yrs due to outward migration to another area and many patients possibly returned to peripheral health care referral doctors for regular follow up.

DISCUSSION: The present study evaluated levels of serum thyroglobulin in response to therapy, tumor recurrence and metastases in patients with differentiated thyroid carcinoma. Response to therapy variables involves data accumulated over months to years after initial therapy. Post-operative serum thyroglobulin prior to radioactive iodine is used as a very early response to therapy marker. The precise cut off values used depends on postoperative Thyroid Stimulating Hormone (TSH)[5,6,7] and the time of surgery.[8,9] Van herle who devised the original assay for thyroglobulin, states that serum thyroglobulin levels higher than 10 ng/ml raises the suspicion of thyroid remnant after thyroidectomy or presence of metastases. Such levels of 35±8.1 ng/ml were noted in the present study in 8 subjects. Serum thyroglobulin levels of <10 ng/ml is reassuring and reflects adequate surgical resection of tumor with either small volume residual disease or normal thyroid bed remnant and not suspicious for malignant tumor.[4] Where as a rising thyroglobulin over time should prompt further evaluation for recurrence in patients treated with less than total thyroidectomy or with total thyroidectomy without radioactive iodine (RAI) remnant ablation.

Serum thyroglobulin levels may be used to detect tumor recurrence as thyroglobulin principally integrates three variables, mass of the thyroid tissue present (benign or malignant), the degree of TSH receptor stimulation and tumor intrinsic ability to synthesize and secrete thyroglobulin. When TSH is low (on levothyroxine (LT_4) therapy) basal serum thyroglobulin may be undetectable (UD). Well differentiated thyroid carcinoma and thyroid remnants display >10 fold serum thyroglobulin response to TSH stimulation.[10] Values as high as 300 ng/ml in recurrence and >1000 ng/ml in subjects with metastases were observed in the present study while in remnant disease a fourfold increase was noted.

Several investigators have reported abnormally elevated serum thyroglobulin levels in patients with negative radioiodine scans.[11,12,13] In the present study four such cases were noted with negative scan and serum thyroglobulin >1000 ng/ml, presented with distant metastases in lungs and bone which seems to be a more sensitive indicator in detecting the presence of distant metastases than radioiodine scans. As stated by a Aiello and Manni[14] Paccini et al[15] suggest that abnormally high thyroglobulin levels may be false positive results due to presence of residual thyroid or metastatic tissue that is not detected by conventional radioiodine scan. Shepherd[16] and Black et al[17] state that serum thyroglobulin may replace radioiodine scans and the need to withdraw thyroxine therapy. Present study concurs with the views of Shepherd and Black that in the follow up of patients with differentiated thyroid cancer, no routine scans are needed as long as serum thyroglobulin remains undetectable but further testing is warranted when detectable thyroglobulin is obtained during thyroxine suppression.

Thyroglobulin assay is technically demanding. False positive or false negative results may be due to over/under estimation by RIA, IRMA (isotopic), ICMA (non-Isotopic) methods; other technical problems include poor interassay precision, hook effect, inter method standardization differences which compromise the clinical utility of serum thyroglobulin estimation.[18,19] In 20% cases of DTC, circulating thyroglobulin auto antibodies cause interference resulting in falsely high or low values. Papageorgiou et al[20] evaluated in a retrospective study, the serum thyroglobulin levels as a marker for recurrence of thyroid cancer and established a postoperative threshold of cutoff value of 1.3 ng/ml to guide patient follow up when thyroglobulin auto antibodies are not estimated or testing is unavailable, for interpreting very high or very low levels of thyroglobulin. However Black et al suggest that thyroglobulin antibodies do not present a significant problem in the correlation between thyroglobulin levels and the status of cancer. Clearly serum Thyrglobulin is of great value in following patient progress after thyroidectomy. Giovanella and Ceriani[21] study found post-surgery thyroglobulin of <3.0 µg/L to be an independent prognostic factor and 93% of their patients were disease free at twelve months. Spencer CA et al[22] observed that serial measurement of basal thyroglobulin concentrations can be used to monitor tumor progression or regression. The development of low i.e <1ng/ml serum thyroglobulin (on LT_4 therapy) by the second post-operative year signifies five year recurrence where as rising serum thyroglobulin in the face of TSH suppression indicates an abnormal response consistent with recurrence. Similar values were observed in the present study, the serum thyroglobulin values at second and fifth year being 0.39 ng/ml and 0.30 (n=12) respectively. Many of these subjects had progression free survival for over ten years.

CONCLUSION: It cannot be overstated that the most useful clinical application of serum thyroglobulin assay is to monitor thyroid cancer patients after total thyroidectomy and radio ablation. Most studies reviewed considered serum Thyroglobulin levels above 10ng/ml to indicate tumor recurrence and metastases and below 10 ng/ml as not suspect for malignancy. Serum Thyroglobulin measurement remains a simple yet valuable parameter and the cornerstone in follow up of patients with differentiated thyroid cancer.

REFERENCES:

1. Tuttle RM. An Overview of the Management of Thyroid Cancer, in a Practical Manual of Thyroid and Parathyroid Disease. 2010. Blackwell Publishing.
2. Boron WF and Boulpaep EL. Medical physiology: A cellular and Molecular approach, page 1300. 2003. Elsevier.
3. Blahd WH. Serum Thyroglobulin in the Management of Thyroid Cancer. J Nucl med 1990; 31: 1771-73.
4. Van Herle AJ, Uller RP. Elevated serum thyroglobulin. A marker of metastases in differentiated thyroid carcinomas. J Clin Invest. 1975; 56: 272-77.
5. Grigsby PW, Siegel BA, Bekker S, Clutter WE, Moley JF Preparation of patients with thyroid cancer for ^{131}I scintigraphy or therapy by 1-3 weeks of thyroxine discontinuation. J Nucl Med. 2004; 45: 567-70.
6. Goldman JM, Line BR Aamodt RL, Robbins J. Influence of triiodothyronine withdrawal time on ^{131}I uptake postthyroidectomy for thyroid cancer. J Clinical Endocrinology & amp Metabolism. 1980; 50: 734-9.
7. Hilts SV, Hellman D, Anderson J, Woolfenden J, Van Antwerp J, Patton D. Serial TSH determination after T3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. J Nucl Med. 1979; 20: 928-32.
8. Welsch M, Abeln M, Zaplatnikov K, Menzel C, Ackermann H, Döbert N, Grünwald F. Multiparameter scoring system for the prognosis of differentiated thyroid cancer. Nuklearmedizin 2007; 46: 257-62.
9. Välimäki M, Lamberg BA. How to deal with undetectable and low measurable serum thyroglobulin levels in the follow-up of patients with differentiated thyroid carcinoma? Acta endocrinologica. 1986; 110: 487-92.
10. Piccardo A, Arecco F, Puntoni M, Foppiani L, Cabria M et al. Focus on high-risk DTC patients: high postoperative serum thyroglobulin level is a strong predictor of disease persistence and is associated to progression-free survival and overall survival. Clin Nucl Med. 2013; 38: 18-24.
11. Blahd WH, Drickman M, Porter CW, Hill VA, Baumgartner WA. Serum thyroglobulin, a monitor of differentiated thyroid carcinoma in patients receiving thyroid hormone suppression therapy: concise communication. J Nucl Med 1984; 25: 673-76.
12. Ashcraft MW, Van Herle AJ. The comparative value of serum thyroglobulin measurements and iodine 131 total body scans in the follow-up study of patients with treated differentiated thyroid cancer. Am J Med. 1981; 71: 806-14.
13. Black EG, Gimlette TMD, Maisey MN, Cassoni A, Harmer CL, Oates GD, Hoffenberg R. Serum thyroglobulin in thyroid cancer. Lancet. 1981; 318: 443-45.
14. Aiello D, Manni A. Thyroglobulin measurement vs. Iodine ^{131}I total: Body scan for follow-up of well-differentiated thyroid cancer. Arch Intern Med. 1990; 150: 437.
15. Pacini F1, Lippi F, Formica N, Elisei R, Anelli S, Ceccarelli C, Pinchera A. Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. J Nucl Med. 1987; 28: 1888-91.

16. Black EG, Sheppard MC, Hoffenberg R. Serial serum thyroglobulin measurements in the management of differentiated thyroid carcinoma. Clin Endocrinol 1987; 27: 115-120.
17. Black EG, Sheppard MC. Serum thyroglobulin measurements in thyroid cancer: Evaluation of "False" positive results. Clin Endocrinol.1991; 35: 519-20.
18. Delom F, Mallet B, Carayon P, Lejeune PJ. Role of extracellular molecular chaperones in the folding of oxidized proteins. Refolding of colloidal thyroglobulin by protein disulfide isomerase and immunoglobulin heavy chain-binding protein. J Biol Chem. 2001; 276: 21337-42.
19. Delom F, Lejeune PJ, Vinet L, Carayon P, Mallet B. Involvement of oxidative reactions and extracellular protein chaperones in the rescue of misassembled thyroglobulin in the follicular lumen. Biochem Biophys Res Commun. 1999; 255: 438-43.
20. Papageorgiou MS, Liratzopoulos N, Minopoulos G, Manolas KJ. Thyroglobulin - what is the postoperative threshold for the suspicion of thyroid cancer recurrence in the absence of anti-Tg antibody measurement? S Afr J Surg. 2011; 49: 118-22.
21. Giovanella L, Ceriani L, Ghelfo A, Keller F. Thyroglobulin assay 4 weeks after thyroidectomy predicts outcome in low-risk papillary thyroid carcinoma. Clin Chem Lab Med. 2005; 43: 843-7.
22. Spencer CA1, LoPresti JS, Fatemi S, Nicoloff JT. Detection of residual and recurrent differentiated thyroid carcinoma by serum thyroglobulin measurement. Thyroid. 1999; 9: 435-41.

AUTHORS:

1. Madhuri Sepuri
2. Prasadula Ashok
3. Shashiprabha K.

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Biochemistry, Andhra Medical College, Visakhapatnam.
2. Assistant Professor, Department of Surgery, Andhra Medical College, Visakhapatnam.
3. Professor, Department of Nuclear Medicine, Andhra Medical College, Visakhapatnam.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Madhuri Sepuri,
Department of Biochemistry,
Andhra Medical College,
Maharanipeta,
Visakhapatnam-530001.
E-mail: smadhurika@yahoo.com

Date of Submission: 01/06/2015.
Date of Peer Review: 02/06/2015.
Date of Acceptance: 07/06/2015.
Date of Publishing: 13/06/2015.