

## RELATIONSHIP BETWEEN SERUM THYROTROPIN LEVEL AND POST-OPERATIVE GOITRE RECURRENCE

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*SUMMARY: Following partial thyroid resection for non-toxic nodular goitre, 309 euthyroid patients were allocated to thyroxine usage and thyrotropin (TSH) level. Thyroid hormones and TSH were evaluated post-operatively every year. Recurrence were investigated with physical examinations, scintigraphy and ultrasonography, and diagnosed with two or three of those tests. We determined the effect of thyroxine and TSH level on the incidence of post-operative goitre recurrence. The incidence of recurrence was found 33.3% in 39 patients regularly taking 0.15 mg/day or more thyroxine, 47.4% in 57 patients regularly taking 0.10 mg/day thyroxine, 66.3% in 83 patients taking thyroxine, irregularly, and 78.5% in 130 patients who did not take any thyroxine. The recurrence was 58.6% in patients with TSH level less than 1  $\mu$ IU/ml, 66.9% in patients with TSH level between 1 to 5  $\mu$ IU/ml, and 62.5% in patients with TSH level more than 5  $\mu$ IU/ml. It was seen that the incidence of recurrence was not diminishing with suppression of TSH level while it was perceptively reduced in the patients who used thyroxine regularly at 0.15 mg/day or more doses as compared to those who use irregularly or not all. We observed that there is no strong relation between post-operative recurrence rate and TSH level. We believe that the thyroxine is necessary in order to prevent post-operative goitre recurrence, but the mechanism of prevention with thyroxine usage may not be TSH suppression.*

*Key Words: Thyroid surgery, recurrence, goitre, thyroxine, TSH.*

### INTRODUCTION

Factors responsible for recurrence of goitre in patients with partially operated thyroid gland because of benign nodular goitre are not well known. The old concept of increased TSH secretion as a main factor in goitrogenesis and recurrences following partial thyroid resection is generally accepted (2,3,5).

In general, thyroid hormone is given to a patient for one or two reasons. Firstly, to replace failing endogenous production of thyroid hormone and secondly, to suppress the patient's own thyroid hormone production via the pituitary thyroid negative feedback system, in order to prevent either goitre formation or reduce goitre size (1, 3, 4, 8, 22). The aim of the wide usage of thyroxine and preventive medication in the post-operative period is the suppression of serum TSH level (8,18, 22,

24, 25, 27). The main objective of this investigation was to establish the relationship between the TSH level and the recurrence rate in patients with thyroid surgery due to non-toxic nodular goitre.

### MATERIALS AND METHODS

A total of 309 patients who had operations due to benign nodular goitre were investigated. The ages of the patients varied between 18 and 71. Of the 309 patients, there were 251 women (mean age: 33.1), and 58 men (mean age: 44.5). The mean duration of post operative observation was 5.4 years.

The types of operative procedures were lobectomy in 46 cases, bilateral near total in 139 cases and unilateral partial thyroidectomy in 124 cases.

The patients were divided into four groups according to their usage of thyroxine in the post-operative period;

Group 1: Patients taking regularly 0.15 mg/day or more thyroxine (39 patients).

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Table 1: The variation of the incidence of post-operative goitre recurrence according to TSH level.

TSH levels	Number of all cases	Number of cases with recurrence
< 1 µIU/ml	70	41 (58.6%)
Between 1 and 5 µIU/ml	151	101 (66.9%)
> 5 µIU/ml	88	55 (62.5%)

Group 2: Patients taking regularly 0.1 mg/day thyroxine, (57 patients).

Group 3: Patients taking thyroxine irregularly (83 patients).

Group 4: Patients who did not take any thyroxine (130 patients).

All patients were investigated with physical examination and scintigraphy for recurrence and for thyroid function (serum TSH, total T<sub>3</sub> and T<sub>4</sub>, free FT<sub>3</sub> and FT<sub>4</sub>) with RIA every year after thyroid resection.

During their last control between 1988-1990, patients were physically examined by two experienced physicians first and then admitted for scintigraphy and finally for ultrasonography. In scintigraphic examination, the patient was given 2 mCi of Tc-99 m pertechnetate intravenously, followed by 15 minutes of 150.000 counts at the neck area, using a pinhole collimator with a Siemens Searle Camera, with the patient in the supine position. After the scintigraphic examination, the patient was examined ultrasonographically, using a Toshiba 32B instrument with a 5 MHz linear transducer. Sonographic pillow was used to increase the resolution. The three examinations taken together decided the incidence of recurrence in the patients.

Serum TSH, total T<sub>3</sub> (TT<sub>3</sub>) and T<sub>4</sub> (TT<sub>4</sub>), free (FT<sub>3</sub>) and (FT<sub>4</sub>) were determined with radio immunoassay kits (Amersham). The normal ranges were; TSH: 0.5 µIU/ml, TT<sub>3</sub> : 0.8-2.7 nmol/L, TT<sub>4</sub> : 62-165 nmol/L, FT<sub>3</sub> : 3.2-8.2 pmol/L, FT<sub>4</sub>: 9b.4-25 pmol/L. They were 70 patients with TSH levels less than 1 uIU/ml, 151 patients with TSH levels more than 5 µIU/ml.

Chi-square tests were applied to compare the four groups and patients with different TSH level.

RESULTS

Any growth or change in the residual thyroid tissue was interpreted as an evidence of recurrence. Recurrence was detected in 197 (63.8%) of the 309 patients. The patients were free from any other endocrine disorders, and had no other medication.

The values of TT<sub>3</sub>, TT<sub>4</sub>, FT<sub>3</sub>, FT<sub>4</sub> of all patients were in normal range.

TSH levels of the 197 patients with recurrence, 41 had less than 1 µIU/ml, 101 had 1 to 5 µIU/ml, 55 had more than 5 µIU/ml (Table 1).

The variation of the recurrence rate with thyroxine intake and TSH level is given in Table 2.

Group 1 consisted of 39 patients. Recurrence was detected at 6(31.2%) of 19 patients with TSH level than 1 µIU/ml, 5(35.7%) of 14 patients with TSH level between 1 and 5 µIU/ml, and 2(33.3%) of 6 patients with TSH level more than 5 µIU/ml in Group 1.

Group 2 consisted of 57 patients. Recurrence was detected at 12 (57.1%) of 21 patients with TSH level less than 1 µIU/ml, 8 (38.1%) of 21 patients with TSH level between 1 and 5 µIU/ml and 7 (46.7%) of 15 patients with TSH level more than 5 µIU/ml in Group 2.

Group 3 consisted of 83 patients. Recurrence was detected at 9 (64.3%) of 14 patients with TSH level less than 1 µIU/ml 33 (71.7%) of 46 patients with TSH level between 1 and 5 µIU/ml, and 13 (56.5%) of 23 patients with TSH level more than 5 µIU/ml in Group 3.

Group 4 consisted of 130 patients. Recurrence was detected at 14 (87.5%) of 16 patients with TSH level less than 1 µIU/ml 55 (78.6%) of 70 patients with TSH level between 1 and 5 µIU/ml, and 33 (75.0%) of 44 patients with TSH level more than 5 µIU/ml in Group 4.

Difference for recurrence rates between three subgroups in Group 1 was not statistically significant (p>0.05). Then were statistically significant difference for recurrence rates between patients with TSH level < 1 µIU/ml and TSH level > 5 µIU/ml in group 2, 3 and 4 (p<0.05).

Table 2: The variation of the incidence of post-operative goitre recurrence according to the thyroxine usage and TSH level.

TSH levels	Number of patients recurrence			
	Group 1	Group 2	Group 3	Group 4
< 1 µIU/ml	6/19 (31.5%)	12/21 (57.1%)	9/14 (64.3%)	14/16 (87.5%)
Between 1 and 5 µIU/ml	5/14 (35.7%)	8/21 (38.1%)	33/46 (71.7%)	55/70 (78.6%)
> 5 µIU/ml	2/6 (33.3%)	7/15 (46.7%)	13/23 (56.5%)	33/44 (75.0%)
Total	13/19 (33.3%)	27/57 (47.4%)	55/83 (66.3%)	102/130 (78.5%)

## DISCUSSION

Recurrence is an important problem following the surgical treatment of nodular goitre. Inadequacy of surgical technique, iodine deficiency, and the decrease in thyroid hormones secretion may play a role in recurrence as well as pathogenetic factors. It has been pointed out that the increase in TSH production through a feed back mechanism leads to growth and structural change of the thyroid gland (2, 3, 6,10,17,29), and fairly high incidence of recurrences following operation for nodular goitre may be accounted for in this manner (3, 5,15,20,22, 30). Some investigators reported that goitre maintenance is not explained by an increased TSH secretion rate (2,7,9,10,22,23) and recurrence may occur without increased TSH (2, 21). Toft *et al.* had found no significant difference of the TSH levels in the patients with diffuse goitre and the non-goitrous controls, and TSH levels in the patients with nodular goitre were significantly lower than those recorded in either the patients with diffuse goitre or in the patients without goitre. They have claimed that the maintenance of goitre was not dependent upon a raised level of plasma TSH level (28). Heinz *et al.* also suggested that goitre in the Cause Valley is not dependent on increased TSH level (29). In the present state of our knowledge, it is not clear that a raised serum TSH level causes the recurrence and implies a need for thyroid replacement therapy (15).

Thyroxine has also been widely used to prevent recurrence in the post-operative period of non-toxic goitre cases (4,6,12,13,24,26,27). The central concept in prophylactic medication with thyroxine against recurrence is considered to prevent goitre growth by suppressing TSH release through pituitary-thyroid negative feed back mechanism (4,8,11,16,22,24). It has been pointed out that 0.15 to 0.20 mg of thyroxine daily could be sufficient to suppress the pituitary thyroid mechanism (3,14,16,18,19, 22, 24). TSH less than 1  $\mu$ U/ml is the target of suppression.

In our study, post-operative goitre recurrence rates were similar in Group 1 patients with different TSH levels. But, patients with TSH level less than 1  $\mu$ U/ml showed higher recurrence rates than patients with TSH level more than 5  $\mu$ U/ml in Group 2, 3 and 4. The incidence of recurrence changed due to the use of thyroxine ( $p < 0.001$ ), and decreased independently from TSH level, when the thyroxine was used regularly with 0.15 mg/day or more doses. We have observed that there was no relation between suppression of TSH level and the decrease of recurrence rate to depend upon thyroxine usage in this study. Nilsson *et al.* pointed out that

even if TSH does not play any role in goitrogenesis, a reduction of the TSH production rate to sub-physiological levels by means of exogenous thyroid hormone may be of importance in diminishing goitre size and preventing goitre formation (22).

Our results indicate that a raised TSH level may not be an indicator of post-operative recurrent goitre and therefore main cause of recurrence. We believe that the thyroxine therapy is necessary in order to prevent goitre formation in Turkey which is an endemic goitre area. It is not known with which mechanism the thyroxine prevents the recurrence.

It is our opinion that the preventive mechanism of post-operative recurrent goitre with thyroxin usage may not be due to the TSH suppression, and more experimental and clinical studies are required to shed light on the preventive mechanism.

## REFERENCES

1. Astwood EB, Cassidy CE, Aurbach ED : Treatment of goitre and thyroid nodules. *JAMA*, 174:459, 1960.
2. Beckers C, Cornette C : TSH production rate in nontoxic goitre. *J Clin Endoc Metab*, 32:852, 1971.
3. Bergfeld G, Risholm L : Post-operative thyroid hormone therapy in non-toxic goitre. *Acta Chir Scand*, 126:531, 1963.
4. Bernstein RS, Robbins J : Intermittent therapy with L-thyroxine. *N Eng J Med*, 281:1444, 1969.
5. Blichert-Toft M, Egedorf J, Chirstiansen C, Axelsson CK : Function of pituitary-thyroid axis after surgical treatment of nontoxic goitre. *Acta Med Scand*, 206:15, 1979.
6. Bulum M, Rothschild M : Improved non operative diagnosis of the solitary "cold" thyroid nodule. *JAMA*, 243:242, 1980.
7. Buttfield IH, Black ML, Hoffman MJ, et al : Studies of the control of thyroid function in endemic goitre in Eastern New Guinea. *J Clin Endoc Metab*, 26:1201, 1966.
8. Clarch HO : Thyroid nodules and thyroid cancer. In *Endocrine Surgery of the thyroid and Parathyroid Glands*. St Louis, CV Mosby Co, pp 56-90, 1985.
9. Cheung P, Boey J, Wong J : Thyroid function after hemithyroidectomy for benign nodules. *World J Surg*, 10:718, 1986.
10. Delange FM, Hershman SM, Erman EM : Relationship between the serum thyrotropin level, the prevalence of goitre and the pattern of iodine metabolism. *J Clin Endoc Metab*, 33:261, 1971.
11. Geerdson JP, Frolund L : Recurrence of non-toxic goitre with and without post-operative thyroxine medication. *Clin Endoc*, 21:529, 1984.
12. Geerdson JP, Frolund L : Thyroid function after surgical treatment of non-toxic goitre. *Acta Med Scand*, 220:341, 1986.

13. Gharib H, Goeliner JR : Evaluation of nodular thyroid disease. In: *Endocrinology and Metabolism Clinics of North America*. Ed by Young FW, Klee GG, Philadelphia, WB Saunders Co, pp 511-526, 1988.
14. Glassfoud GH, Fowler EF, Cole WH : Treatment of nontoxic nodular goitre with desiccated thyroid. *Results of Evaluation Surgery*, 58:621, 1965.
15. Griffisiths NS, Murley RS, Gulin R, Simpson RD, Woods TF, Burnett D : Thyroid function following partial thyroectomy. *Br J Surg*, 61:626, 1974.
16. Hoffman DP, Surks MI, Oppenheimer JH, Weitzman ED : Response to thyrotropine relasing hormone, an objective criterion for the adequacy of thyrotropine suppression therapy. *J Clin Endoc Metab*, 44:892, 1977.
17. Kologlu S : Euthyroid goitre. *Clinics of Turkey*, 4:299, 1984.
18. Kologlu S, Baskal N, Uysal AR, Kologlu B : The value of L-thyroxine suppression therapy in the prevention of post-thyroidectomic recurrences. *J Ankara Medical School*, 10:467, 1988.
19. Krugmann LG, Hersmann JM : TRH test as an index of suppression compared with thyroid radio-iodine uptame in euthyroid goitrous patients treated with thyroxine. *J Clin Endoc Metab*, 47:78, 1978.
20. Matte R, Ste-Marie LG, Comtois R, et al : The pituitary-thyroid axis after hemithyroidectomy in euthyroid man. *J Clin Endoc Metab*, 53:377, 1981.
21. Murley RS, Rigg BM : Post-operative thyroid function and complications in relation to a measured thyroid remnant. *Br J Surg*, 55:757, 1968.
22. Nilsson G, Petersson U, Levin K, Hughes R : Studies on replacement and suppressive dosages of L-thyroxine. *Acta Med Scand*, 202:257, 1977.
23. Ogihara T, Yamamoto T, Fukuchi M, Oki K : Serum thyrotropin levels of natives in Sarawak, Bornea Island. *J Clin Endoc*, 35:711, 1972.
24. Perrild H, Hansen JM, Hegedus, et al : Tri-iodothyronine and thyroxine treatment of diffuse non-toxic goitre evaluated by ultrasonic scanning. *Acta Endoc*, 100:382, 1982.
25. Rojeski MT, Gharib H : Nodular thyroid disease. *New Eng J Med*, 313:428, 1985.
26. Roher HD, Goretiki PE : Management of goitre and thyroid nodules in an area of endemic goitre. In *Surgical Clinics of North America Endocrine Surgery*. Ed by Clark O, Weber AC, Philadelphia, WB Saunders Co, p 233, 1987.
27. Sekadde CB, Slaunwhite WR, Aceto T, Murray K : Administration of thyroxine once a week, *J Clin Endoc Metab*, 39:759, 1974.
28. Toft AD, Irvine WJ, Hunter WH : A comparison of plasma TSH levels in patients with diffuse and nodular non-toxic goitre. *J Clin Endoc Metab*, 42:973, 1978.
29. Wahner HW, Mayberry WE, Gaitan EJ : Endemic goitre in the Cagua Valley. *J Clin Endoc Metab*, 32:491, 1971.
30. Young RL, Harvey WC, Mazzeferri EL, Reynolds CS, Hamilton CR : Thyroid stimulating hormone levels in idiopathic euthyroid goitre. *J Clin Endoc Metab*, 41:21, 1975.

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