HYPOTHYROIDISM FOLLOWING THYROID SURGERY

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Abstract- Postsurgical hypothyroidism and its incidence has not been fully investigated. In this study, the incidence of hypothyroidism and its possible risk factors at Shariati Hospital was assessed. One hundred and two patients with benign thyroid diseases, who had undergone thyroidectomy, were investigated with regards to thyroid function profile during period of one year after the operation every three months with post-operative sample as the baseline. Hypothyroidism was developed in 36 patients (35.2%) on average 5 ± 3.2 months after surgery. Factors such as increased age, operation type, histopathologic type, underlying disease, lymphocytic infiltration and use of levothyroxine before surgery were associated with the increased incidence of hypothyroidism. It seems that use of indicators such as Graves' disease and lymphocytic infiltration in pathologic specimens should be helpful in projecting the potential occurrence of hypothyroidism in patients undergoing thyroidectomy.

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INTRODUCTION

Hypothyroidism is a syndrome caused by thyroid hormone deficiency. Autoimmune thyroiditis and iatrogenic mechanisms such as radioactive iodine therapy and thyroidectomy are the most common causes of hypothyroidism (1). The incidence and the time of the occurrence of hypothyroidism following thyroidectomy are not fully investigated. According to previous studies the incidence of hypothyroidism after lobectomy-ismechtomy is up to 36 percent (2). The most common cause of hypothyroidism after thyroid operation is subtotal resection for Graves' disease or multinodular goiter but autoimmune destruction of the thyroid tissue is another important cause for post operative hypothyroidism (3).

According to previous studies patient's age, gender, body surface, premedicative T3 and T4, preoperative antithyroglobulin antibody and thyrotropin-binding immunoglobulins level, and weight of removed thyroid tissue have no effect on the occurrence of hypothyroidism (4). Remnant tissue size seems to be important in prediction of outcome of operation, but within optimal remnant size the only factors which are effective on the risk of hypothyroidism are lymphocytic infiltration of the thyroid tissue and antithyroid microsomal antibody titer (4, 5). With optimal remnant size the higher the antithyroid microsomal antibody titer and the degree of lymphocytic infiltration, the greater the likelihood of post operative hypothyroidism (5).

Hypothyroidism as a sequel of thyroidectomy remains unnoticed most of the time (6). Mild

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hypothyroidism after subtotal thyroidectomy may subside after a few months as the remnant thyroid tissue is stimulated by the rising TSH. Furthermore, post-operative hypothyroidism in patients who had chronic hypothyroidism and do not receive hormone replacement therapy early after operation can be severe and fatal (7).

This study aims to show the pattern and the incidence rate of hypothyroidism after different types of operation on thyroid gland.

MATERIALS AND METHODS

A total of 102 patients admitted to the surgery ward of a major referral hospital (Dr. Shariati Hospital affiliated to the Tehran University of Medical Sciences) during one year from July 2001 to January 2003 were included in this cross sectional study.

Criteria for entering the study were being scheduled for lobetomy-isthmectomy, subtotal thyroidectomy or near total thyroidectomy operation and being euthyroid. Patients with past history of hypothyroidism and any patient with malignant pathology were excluded. During one week after the operation, blood samples were obtained from patients undergone any type of thyroidectomy (lobectomy-isthmectomy, subtotal and total thyroidectomy), who consented to enter the study and were sent to the laboratory for thyroid function tests (TFT). TSH was measured by immunoradiometric assays (Kavoshyar, Iran). Serum T3 and T4 were evaluated using commercially available radioimmunoassay kits (Kavoshyar, Iran). The inter assay CV were 7.5% for TSH, 5% for T4, and 6% for T3, and intra assay CV were 6.9% for TSH, 5.4% for T4, and 6.8% for T3.

During the first three months after surgery, all patients were visited monthly, then 2 monthly and then on a 3-monthly basis. In each visit TFT of each patient was repeated and registered. Signs and symptoms of hypothyroidism were also investigated in each visit and recorded when present.

The patients were educated on the clinical picture; they were advised to counsel the department once any symptoms indicating hypothyroidism would occur. Once hypothyroidism was established in a patient, hormone replacement therapy was started. Such patients were then being visited on a monthly basis. The drug dosage was adjusted to the serum level of TSH. When TSH returned to normal range, the replacement therapy was being continued for a period of three months; the therapy was then being suspended for one month to check whether thyroid function has returned to normal.

Primary disease classification

1. Toxic multinodular goiter (TMNG): primary hyperthyroidism associated with longstanding multinodular goiter.

2. Nontoxic multinodular goiter: any non-neoplastic or non-inflammatory nodular enlargement of thyroid gland which is not associated with thyrotoxicosis or myxedema at presentation.

3. Graves' disease: hyperthyroidism associated with diffused goiter or ophthalmopathy or dermopathy.

4. Solitary nodule: nodule of greater than 1 centimeter not associated with multinodular goiter.

Goiter evaluation

A clinical examination was performed for the presence of goiter, using a simplified score, where 0 was no goiter, Ia was a thyroid gland palpable but not visible with extended neck, Ib palpable and also visible on extension, II was an easily recognizable and clearly enlarged thyroid with the head in normal position, III was a large goiter visible at a distance, and IV was very huge thyroid.

Pathologic definitions

1. Graves' disease: mild to moderate symmetric diffuse thyroid enlargement with hyperplastic follicles and prominent papillary in folding, pale colloid. The stroma contains aggregates of lymphoid tissue.

2. Diffuse nontoxic (simple) goiter or colloid goiter: The follicles are lined by crowed columnar cells, which may pile up and form projections similar to those seen in Graves' disease. The stimulated follicular epithelium may involutes to form an enlarged, colloid-rich gland (colloid goiter).

3. Nodular hyperplasia (nodular or multinodular goiter, adenomatous hyperplasia): enlarged thyroid, with multiple nodules. Secondary changes in the

form of hemorrhage, calcification cystic degeneration and atrophy are common (8).

Presence and the degree of lymphocytic infiltration were always inquired from the pathologists. The degree of infiltration was graded as: 1) scattered lymphocytes and other inflammatory cells; 2) moderate number of lymphocytes in the microscopy without the occurrence of germinal center; and 3) occurrence of germinal center (the diagnostic clue of lymphocytic thyroiditis).

Performance of thyroid operations by different surgeons and also suspension of hormone replacement therapy for one month instead of six weeks to determine the thyroid function status were among the drawbacks of our study.

Collected data were compared by statistical tests (including Fisher's exact test and *t* test) and the significance of data was at the level of $P < 0.05$. For some of the variables, relative risks of occurrence of hypothyroidism were estimated and significant level of 95% was determined. These results had been tested in multivariate analysis and similar results had been found.

The study was conducted on an outpatient basis according to the principles of the Declaration of Helsinki and was approved by the medical ethics review board of the Endocrinology and Metabolism Research Center (EMRC) of Tehran University of Medical Sciences (TUMS). Informed consent was obtained from all volunteers after oral and written information had been given.

The gathered data were finally entered the computer. Analysis of data was done using SPSS 10 program.

RESULTS

A total of 72 females (71%) and 30 males (29%) with mean age of 39 ± 13.6 were included. Mean age of females was 38.4 ± 5.1 and mean age of males was 40.5 ± 14.2 years. Based on clinical diagnosis, 18 cases of toxic multinodular goiter (17.6%), 32 cases of non-toxic multinodular goiter (31.3%), 45 cases of solitary nodule (44.1%) and 7 cases of Graves' disease (6.8%) were recognised.

Clinical examination showed 10 cases of grade Ib (9.8%), 36 cases of grade II (35.2%), 44 cases of grade III (43.1%) and 12 cases of grade IV (11.7%) thyromegaly.

Three types of surgical procedures were used including: lobectomy-isthmectomy (45 cases, 44.1%), subtotal thyroidectomy (50 cases, 49%) and near total thyroidectomy (7 cases, 6.8%).

Multinodular goiter was found in 95 cases (93.1%) and 7 cases of Graves' disease (6.9%) were reported by pathology. Lymphocytic infiltration was shown in 36 pathologic specimens (35.2%) including 10 cases of 1+ (9.8%), 6 cases of 2+ (5.8%) and 20 cases of 3+ (19.6%) lymphocytic infiltrations.

The mean duration of disease before operation was 5.5 ± 4.79 years. 46 had used thyroxin for thyroid suppression before operation (45%). 20 patients developed asymptomatic hypocalcemia after the operation (19.6%) and 12 developed symptomatic post operative hypocalcemia (11.7%). one patient developed hematoma at the incision site.

During the one year follow up, hypothyroidism occurred in a total of 36 patients (35.3%; 25 females and 11 males). Overt hypothyroidism however, was present in only 11 patients and the other 25 had sub clinical disorder. In 19 patients, hypothyroidism was persistent and 17 cases experienced transient hypothyroidism. The mean period of occurrence of hypothyroidism was 5 ± 3.2 months.

Of the cases who developed hypothyroidism 25 were female and 11 were male which did not show a significant difference in the risk of developing hypothyroidism (RR= 0.95; CI 95%: 0.64-1.42).

The mean age of the patients who developed hypothyroidism was 44.6 ± 13.9 years and of those who did not develop the disorder were 38.7 ± 14 years. This difference was significant statistically ($P < 0.05$).

Hypothyroidism was seen in 10 patients (55.5%) with toxic multinodular goiter, 12 patients (37.5%) with nontoxic multi nodular goiter, 9 cases (20%) of solitary nodule and 5 cases (71%) with Graves' disease which have shown a significant difference statistically ($P < 0.006$).

Table 1. Significant variables of the study

Variables		Hypothyroid		Non Hypothyroid		Significance level
		Frequency	Percent	Frequency	Percent	
Primary Diagnosis						
	Toxic multinodular goiter	10	55.5	8	44.5	0.006
	Non-toxic multinodular goiter	12	37.5	20	62.5	
	Single nodule	9	20	36	80	
	Graves' Disease	5	71	2	29	
Type of the operation						
	Lobetomy isthmectomy	8	17.7	37	82.3	0.0004
	Subtotal thyroidectomy	22	44	28	56	
	Near total thyroidectomy	6	85.7	1	14.3	
Pathologic Diagnosis						
	Multinodular Goiter	30	31.6	65	68.4	0.007
	Graves' Disease	6	85.7	1	14.3	
Lymphocytic infiltration						
	With infiltration	23	63.9	13	36.1	0.0000
	Without infiltration	13	19.6	53	80.4	
Clinical Diagnosis						
	Grade Ia	0	0	0	0	0.288
	Grade Ib	2	20	8	80	
	Grade II	10	27.7	26	72.3	
	Grade III	20	45.4	24	54.6	
	Grade IV	4	33.3	8	66.7	
History of taking Levothyroxine						
	+	26	56.2	20	438	0.00005
	-	10	17.8	46	82.2	

8 patients (17.7%) who went under lobectomy-isthmectomy, 22 patients (44%) who went under subtotal thyroidectomy and 6 patients (85.7%) who went under near total thyroidectomy developed hypothyroidism (subtotal thyroidectomy versus lobectomy-isthmectomy: RR=2.48, CI 95%: 1.567-3.392), (near total thyroidectomy versus lobectomy-isthmectomy: RR = 4.82, CI 95%: 0.506-45.925).

According to pathology diagnosis, 30 cases (31.6%) of multinodular goiter and 6 cases (85.7%) of Graves' disease became hypothyroid after the operation. ($P < 0.007$)

According to thyroid physical exam, 2 patients (20%) with grade Ib of thyromegally, 10 patients (27.8%) with grade II thyromegally, 20 patients (45.4%) with grade III thyromegally and 4 patients (33.3%) with grade IV thyromegally developed hypothyroidism which did not show a significant statistical difference ($P < 0.288$).

The mean blood level of TSH in patients who developed hypothyroidism was 1.12 ± 0.56 mu/l comparing 0.99 ± 0.7 mu/l in patients who did not develop hypothyroidism. Again this figure did not show a significant statistical difference ($0.1 < P < 0.5$).

Pathologic specimen of 36 patients showed lymphocytic infiltration (35.2%), of these patients 23 developed hypothyroidism (63.8%). Pathologic specimens of 66 patients did not show lymphocytic infiltration and of these 13 patients became

hypothyroid (19.6%) which has shown a significant difference statistically. (RR = 3.24, CI 95%: 1.30-8.06).

The mean duration of the disease before operation among patients who developed hypothyroidism was 7.2 ± 3.5 years compared to 4.8 ± 2.7 in patients who did not develop hypothyroidism which showed a significant difference ($P < 0.01$).

46 patients were on levothyroxine before the operation and of these 26 (56.2%) became hypothyroid after the operation. Of 56 patients who were not on thyroid hormone therapy before the operation 10 (17.8%) developed hypothyroidism which showed a significant difference ($P < 0.00005$).

32 patients developed complication after the operation (hypocalcaemia and hamatoma at the site of operation). Of these, 15 (46.8%) developed hypothyroidism. Of 70 patients who did not develop any complication after the operation 21 (30%) became hypothyroid. This difference was not significant statistically ($P > 0.1$).

Table 1 summarizes the results of the study.

DISCUSSION

Hypothyroidism is a syndrome caused by deficient thyroid hormone secretion. Main subtypes of hypothyroidism include autoimmune thyroiditis and iatrogenic (as occurs following thyroidectomy).

The rate of the post-operative hypothyroidism is usually overestimated by researchers, as they do not consider gradual improvement in thyroid function after operation (1). Prescription of thyroid hormone following thyroidectomy to the patients aims not only to control hypothyroidism but to prevent the recurrence of the primary disease (suppressive therapy).

Of course, thyroid function remains normal in many patients following operation, which obviates replacement therapy. In adult patients with mild hypothyroidism, it is recommended to stop replacement therapy for 1 to 2 months so as to distinguish between persistent and transient hypothyroidism (3).

A number of risk factors have been described which could predict the development of post-thyroidectomy hypothyroidism.

In the current study, among the studied factors, the occurrence of post-thyroidectomy hypothyroidism was not linked with gender of the patients, but had positive association with the age of patients. This finding concurs with the higher incidence of hypothyroidism and positive anti-thyroid antibodies in advanced age. At least one other study has reported similar findings (9).

Among the primary diseases leading to thyroidectomy, Graves' disease and toxic multinodular goiter had the largest influence on the risk of hypothyroidism in our study. The risk of hypothyroidism after subtotal thyroidectomy for toxic multinodular goiter is lower than for Graves' disease.

Subtotal thyroidectomy for nontoxic goiter is usually performed for multinodular goiter and is not typically followed by hypothyroidism, though, a small percentage of the patients develop transient sub-clinical hypothyroidism. Of course, there are reports of transient sub-clinical hypothyroidism after hemithyroidectomy for single nodules (10). Patients who undergo surgery for thyroid nodules do not usually develop persistent hypothyroidism unless most of the thyroid tissue is removed or the remnant tissue does not function normally (11).

In our study duration of the disease was also positively related with the risk of hypothyroidism in the patients. It is probable that longstanding goiter or chronic autoimmune mechanisms lead to fibrotic changes that eventually increase the risk of hypothyroidism.

No relationship was observed between post-operative complications (hypocalcaemia and hamatoma at the site of operation) and the incidence of hypothyroidism. However, the pathology of the thyroid tissue had a role in determining the risk of hypothyroidism. The risk of hypothyroidism was higher in patients with diagnosis of adenomatous goiter and Graves' disease. Grade of the thyromegally on physical examination had no effect on this risk. TSH levels measured shortly after operation was not a prognostic factor for

hypothyroidism. A study in Japan has reported that thyrocyte response to TSH is correlated with post-operative thyroid status (12). Transient increase in TSH, with peak levels 3 to 6 months after the operation, has been detected after thyroid resection. Of course, pituitary thyroid axis does not return to normal function until one year after the operation (13). Serum TSH values typically return to normal 24 months after the operation. TSH levels, however, remains slightly high in patients with bilateral operation and lymphocytic infiltration (14).

The lymphocytic infiltration of the thyroid tissue in pathologic specimens was an important risk factor for post-thyroidectomy hypothyroidism where the strongest association was found. This finding has also been reported in other series (9). It seems advisable to resort to early hormone replacement therapy in patients with lymphocytic infiltration before development of the signs and symptoms of hypothyroidism.

In the current study, the type of the operation had influenced the risk of post operative hypothyroidism. It was also shown that subtotal thyroidectomy increases the risk of hypothyroidism by 2.5 folds.

According to one study, the risk of hypothyroidism after subtotal thyroidectomy for hyperthyroidism was 7.4 to 10.8 percent and large thyroid remnant did not prevent from hypothyroidism (15). Another study on patients with Graves' disease who had undergone operation showed that hypothyroidism was more frequent in patients who had undergone total lobectomy or subtotal lobectomy on the other site and in the case of large lymphocytic infiltration (16).

Most of the cases of hypothyroidism after subtotal thyroidectomy occur in the first year after the operation. After that the incidence increases 1 to 2 percent annually. In patients who remain euthyroid after the operation the incidence of hypothyroidism increases about 0.5 to 1 percent annually which continues until 1 to 2 year after operation and probably is the result of autoimmune destruction of the remnant tissue (11).

In some patients early transient hypothyroidism is developed and subsides after some months (3). The risk of occurrence of transient hypothyroidism after subtotal thyroidectomy for Graves' disease is estimated to be about 20 percent (10) but, some studies have shown that the risk of transient hypothyroidism after Graves' disease can be much higher and about 87.5 percent of patients can develop hypothyroidism, all within the first year (17). It occurs mostly in the first 3 months after the operation and subsides after 6 months (10). Eventually, long after subtotal thyroidectomy for Graves' disease, 3/4 of patients develop hypothyroidism and only 1/4 remain euthyroid (18).

A study in USA on 71 euthyroid patients who underwent hemithyroidectomy and were in euthyroid status following operation, eventually 35 percent of the patients developed hypothyroidism including 16 cases of subclinical and 9 cases of overt hypothyroidism. No significant difference was found between the two groups with regards to age, gender and weight of the removed thyroid tissue (2).

In the current study, hypothyroidism was seen in 17.7 percent of patients who underwent lobectomy isthmectomy. It could therefore be expected that hypothyroidism might occur even after any type of operation. The difference between rates hypothyroidism in reports from the USA and the current study can be attributed to the higher prevalence of thyroiditis in the USA. Another interpretation can be the different iodine supplementation programs between the two countries during the last decade. Regional variations in the prevalence of post operative hypothyroidism has been studied in a study in Iceland and Northeast Scotland which showed lower risk of hypothyroidism in areas of high iodine intake (19).

A study in the USA reported that the incidence of hypothyroidism had no relationship with age, gender and weight of the removed tissue and all the cases of hypothyroidism appeared during first 2 months after operation but in our study age of the patients is one of the involving factors in developing hypothyroidism. As mentioned it can be due to increase in the risk of developing hypothyroidism and the occurrence of positive anti-thyroid antibodies with increasing age.

In 2001, 225 patients with nontoxic multinodular goiter, who had undergone lobectomy, subtotal or total thyroidectomy, were studied in Italy. The incidence of hypothyroidism in the lobectomy group

was 9.1 percent and in the remaining patients was 46.9 percent. The incidence of hypothyroidism after subtotal and total thyroidectomy was not reported individually (11). The rate of hypothyroidism after lobectomy was comparably higher than the present study.

In another study in Italy, post operative hypothyroidism was surveyed retrospectively. It was shown that 44 % of cases of thyroidectomy developed hypothyroidism. Prevalence of hypothyroidism was 6 times higher in patients older than 60. The predictive factors were lymphocytic infiltration and positive serology for antithyroid antibodies (9). Likewise, age and lymphocytic infiltration were among predictive factors in present study.

In conclusion, it seems necessary to design a longitudinal study on occurrence of post-operative hypothyroidism to determine the pertinent risk factors. In particular, age, Graves' disease, lymphocytic infiltration in pathologic specimen, and size of removed thyroid tissue should be investigated.

Conflict of interests

The authors declare that they have no competing interests.

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