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ORIGINAL ARTICLE

Post-hemithyroidectomy hypothyroidism in non autoimmune thyroiditis patients: Incidence, risk factors and duration of follow up

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KEYWORDS
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Summary *Background:* Hemithyroidectomy has a known but less predictable sequelae of hypothyroidism. Presence of anti-thyroid antibody is known, well studied risk factor. Other postulated risk factors include higher pre-operative TSH level and lower ratio of post-operative thyroid remnant to the patient's weight. We reviewed our data to address the above mentioned risk factors.
Method: This was a retrospective study done in National Cheng Kung University Hospital, Taiwan from 2015 to 2017. 125 patients underwent hemithyroidectomy, but 24 patients were excluded due to autoimmune thyroiditis, which was determined as the exclusion criteria. Standard panel of blood investigations were taken in each clinic visit before and after operation. A neck ultrasound was done 2 months post-operatively to assess the thyroid remnant. Chi-square test was used for categorical data analysis. Independent student t-test was used for continuous data with parametric distribution and Mann–Whitney U test for non parametric data. $p < 0.05$ was taken as statistically significant.
Result: The mean duration of follow up was 29.3 months. 4 out of 101 patients had clinical hypothyroidism; 23 patients developed subclinical hypothyroidism post-hemithyroidectomy. 6 patients of subclinical hypothyroidism had spontaneously recovered within 1 year. Pre-operative TSH >2.0 uIU/mL was a risk factor as Chi square test showed $p < 0.001$. However, thyroid remnants were found not to be a risk factor with the Mann–Whitney U test of $p = 0.928$.

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Conclusion: Minimum 1 year of follow up for hemithyroidectomy patients was suggested in order not to miss patients developing hypothyroidism post-operatively.

1. Introduction

Hemithyroidectomy either for benign or occult malignant disease, has a known but rather less predictable sequelae of hypothyroidism. It involves removal of a unilateral thyroid lobe with isthmus and when present pyramidal lobe. The reported incidence of post-hemithyroidectomy hypothyroidism ranges from 0% to 43%,[1,7] with a meta-analysis reporting pooled risk of 22%.[1] The wide range of reported incidence results from a lack of standardized follow-up duration and definition of hypothyroidism. Hypothyroidism in post-hemithyroidectomy can either be subclinical (high TSH with normal free T4/T3) or clinical (low free T4 and T3 with high TSH). There is a much higher incidence of subclinical compared to clinical hypothyroidism.[1,9]

The mean time from surgery to detection of hypothyroidism varies between studies and ranges from four to eight months. About 90% of patients who develop hypothyroidism is detected within first year post-surgery.[2–4,7,9] It has been postulated that the high post-operative TSH level detected in some patient will progressively normalise up to 12 months. Hence the final state of thyroid function can only be determined at 12 months from surgery.[1] Risk factors for hypothyroidism has been delineated by multiple studies, including higher in normal range of pre-operative TSH level, presence of anti-thyroid antibody, lymphocytic infiltration of the gland and lower ratio of the remaining thyroid weight to the patient's weight (derived weight index).[1,4,9] A combination of either these factors carries a higher predictive value for post-operative hypothyroidism comparing to either one alone.[1,4]

One of the well-studied risk factor is pre-operative TSH level. The higher the pre-operative TSH translates to increase risk for development of hypothyroidism post-hemithyroidectomy. However, a definite cut off point has not been established, which might be due to laboratory variation of different studies.

Derived weight ratio, a proportion of thyroid remnant lobe (as calculated from ultrasonographic dimensions) to the body weight, is a predictor of the post-operative thyroid status. A derived ratio lower than 0.08 g/kg is associated with higher incidence of post-operative hypothyroidism.[1]

Age, gender, family history of thyroid disease and primary thyroid pathology are reported not influencing the outcome on thyroid function for patients undergoing hemithyroidectomy.[1,4–6]

In our study, we looked into 125 patients with hemithyroidectomy being done between 2015 and 2017, for the risk factors that could predict post-operative hypothyroidism, particularly the pre-operative TSH level and the thyroid remnant tissue post-operatively.

2. Methodology

This was a retrospective observational study done in National Cheng Kung University Hospital, as a tertiary referral centre in Taiwan, from 1 January 2015 to 31 December 2017. All patients who had undergone hemithyroidectomy were included, both benign thyroid disease as well as thyroid cancer that not required completion thyroidectomy. All the patients were followed up for minimal of one year. Exclusion criteriae were those not consented, defaulted follow up, pre-operatively hypothyroidism or hyperthyroidism, thyroiditis either anti-thyroperoxidase (ATO) positive, thyroglobulin antibody positive or final histopathology of thyroiditis, and those with thyroid cancer that had undergone completion thyroidectomy.

All patients had the similar panel of blood investigations done pre-operatively and two months from the day of surgery, namely TSH, total T4, T3, thyroglobulin, thyroglobulin antibody, and ATO. Total T4 was used instead of free T4 because it was easily accessible with quick result from our hospital laboratory, and it had a good correlation with patients' clinical condition.[26–28] Anti TSH receptor antibody was not measured. An ultrasound neck was done during the follow up to assess the dimension of thyroid tissue. The remnant thyroid volume was derived directly from the ultrasound with the readily available three-dimensional elliptical measurement in the machine. The weight of thyroid gland was calculated with the assumption that 1 cm^3 of thyroid tissue to be weighing 1 g.[24,25] After that, the weight index (weight of the thyroid remnant in gram Vs the total body weight of the patient in kilogram) was reckoned. All these patients were subsequently followed up by the same surgeon bi-monthly with thyroid function test being performed in each follow up.

Hypothyroidism was defined as subclinical (high TSH with normal T4/T3) or clinical (low T4 and T3 with high TSH). Those patients presented with clinical hypothyroidism were given levothyroxine, however no treatment was initiated on those with subclinical hypothyroidism. Our normal TSH value was 0.27—4.20 uIU/mL and normal T4 value was 5.10—14.10 ug/dL.

For data analysis, chi-square test was used for categorical data. For continuous variables, Kolmogorov—Smirnov (KS) test was used to determine whether the distribution was normal. Independent student t-test was used for the continuous data with parametric distribution and Mann—Whitney U test for non parametric data.

3. Results

Total of 125 patients had undergone hemithyroidectomy within the 3-year duration. 105 of them were female and 20

were male. The youngest patient was 13 years old and the oldest was 82 years old. The mean age was 48.8 years old. 51 patients underwent left hemithyroidectomy while right hemithyroidectomy was performed in 74 patients. The majority of the patients, 82 out of 125, were nodular goitre. 14 were follicular adenoma, 4 of them had microscopic papillary thyroid cancer and one was diagnosed to have follicular carcinoma. 24 patients who had autoimmune thyroiditis were excluded from the study. The final number of patients involved in the study was 101 patients (Table 1).

The mean follow up duration was 29.3 months. 78 of the 101 patients were euthyroid post operatively (77.2%). Among those euthyroid, 9 had follicular adenoma, 67 nodular goitre, 1 microscopic papillary thyroid cancer and 1 had low risk follicular carcinoma that only left hemithyroidectomy being performed. The remaining 23 patients developed hypothyroidism (22.8%), 15 of them had nodular goitre, 3 had microscopic papillary thyroid cancer and 5 had follicular adenoma. The majority of patients progressed into hypothyroidism within 3 months post operatively (19 over 23 patients). All these 19 patients had subclinical hypothyroidism. The other four patients suffered from hypothyroidism six to eight months after surgery. All these four patients showed clinical hypothyroidism that required levothyroxine. Among the 78 patients who were euthyroid post-operatively, four of them became subclinical hypothyroidism six months later. The mean duration of developing hypothyroidism is 3.6 months. After follow up of six months duration, six of the subclinical hypothyroidism patients demonstrated spontaneously recovered, with normal thyroid function test. The mean duration of spontaneous recovery was 8.7 months (Fig. 1).

The size of the thyroid remnant was measured by ultrasound two months post operatively. Then the "thyroid index" was calculated by dividing the remnant weight by the body weight of the patient (g/kg). In the euthyroid group, weight of the thyroid remnant ranged from 2.28 g to 37.9 g, with the median of 6.36 g. In the contrary, the hypothyroid group had the thyroid remnant weight of 2.20 g—18.14 g, with the median of 3.55 g. The median of the thyroid index was 0.112 g/kg and 0.067 g/kg for the euthyroid group and the hypothyroid group respectively. Mann—Whitney U test was used because the data is non parametric. The p value obtained was = 0.928 (>0.05), which was not significant statistically.

Table 1 Demographic of patients.

Demography	Patients, n = 101
Age	13-82 (mean = 48.0)
Sex	
Male	18 (17.8%)
Female	83 (82.2%)
Site of hemithyroidectomy	
Right	62 (61.4%)
Left	39 (38.6%)
Histology	
Nodular goitre	82 (81.2%)
Follicular neoplasm	15 (14.8%)
Papillary microcarcinoma	4 (4.0%)
Interval of operation to hypothyroidism (months)	1.5—12 (mean = 3.6)

In our study, we discovered that significant amount of patients with pre-operative TSH of >2.0 uIU/mL developing post-operative hypothyroidism. In the euthyroid group, the pre-operative TSH value ranged from 0.005 to 3.26 uIU/mL, with the mean of 1.176 uIU/mL. Meanwhile, the pre-operative TSH level for the hypothyroid group varied between 0.14 and 3.93 uIU/mL, with the mean of 2.360 uIU/mL. Chi square test revealed $p < 0.001$, signifying that pre-operative TSH of >2.0 uIU/mL as a risk factor of post-hemithyroidectomy hypothyroidism (Table 2).

We measured total T4 and T3 in all patients. Out of 101 patients, only 6 of them showed marginally low T3 with the normal T4 level pre-operatively. Post-operatively, the T3 level also concordant to the T4 level.

4. Discussion

Hypothyroidism is a known complication after hemithyroidectomy, with the commonest cause being reported as autoimmune thyroiditis. The overall incidence was about 22% with some of the studies demonstrating value as high as 55.8%.[1—7] From our data, we had 24.8% of patients developing hypothyroidism post hemithyroidectomy, which was similar to other studies[1,7,9] We hypothesized that there are other components which may contribute to the development of hypothyroidism in these patients. Therefore, our study aimed to look for these factors, such as pre-operative TSH levels and remnant thyroid volume.

We concluded that pre-operative TSH level of ≥2.0 mU/L being a strong predictive factor of post hemithyroidectomy hypothyrodism with the p value of <0.001. Various data derived from retrospective studies had shown that a pre-operative TSH level higher than 2.0mU/L was associated with higher chance for post-operative hypothyroidism.[3,5] A prospective study of 109 patients, reported post-operative hypothyroid patients had had a pre-operative TSH level greater than 1.4mU/L.[1] A pre-operative TSH of more than 2.6mU/L was an independent factor for permanent post-op hypothyroidism.[3,6] Our patients with permanent hypothyroidism had pre-operative TSH ranging from 0.14 mU/L to 3.93 mU/L, with the mean of 2.56 mU/L (<2.6 mU/L).

Some authors believed that the derived weight ratio of thyroid gland influenced the incidence of post operative hypothyroidism,[1] but the others concluded differently.[4,7—12] There were also arguments between total thyroidectomy or subtotal thyroidectomy for patients with hyperthyroidism,[14—17] as the authors deduced that the thyroid remnant affecting the post operatiave thyroid function. We were unable to demonstrate that the remnant thyroid volume as one of the factor that determining post operative hypothyroidism. Our p value for derived thyroid weight index was 0.928, which was statistically insignificant.

The reported incidence of occult malignancy was 3—9% after hemithyroidectomy for benign thyroid nodule.[12] Hemithyroidectomy was the choice of treatment in micropapillary thyroid cancer and low risk follicular thyroid cancer.[18,19] We had four patients of occult papillary thyroid cancer, three of them progressing into hypothyroidism after

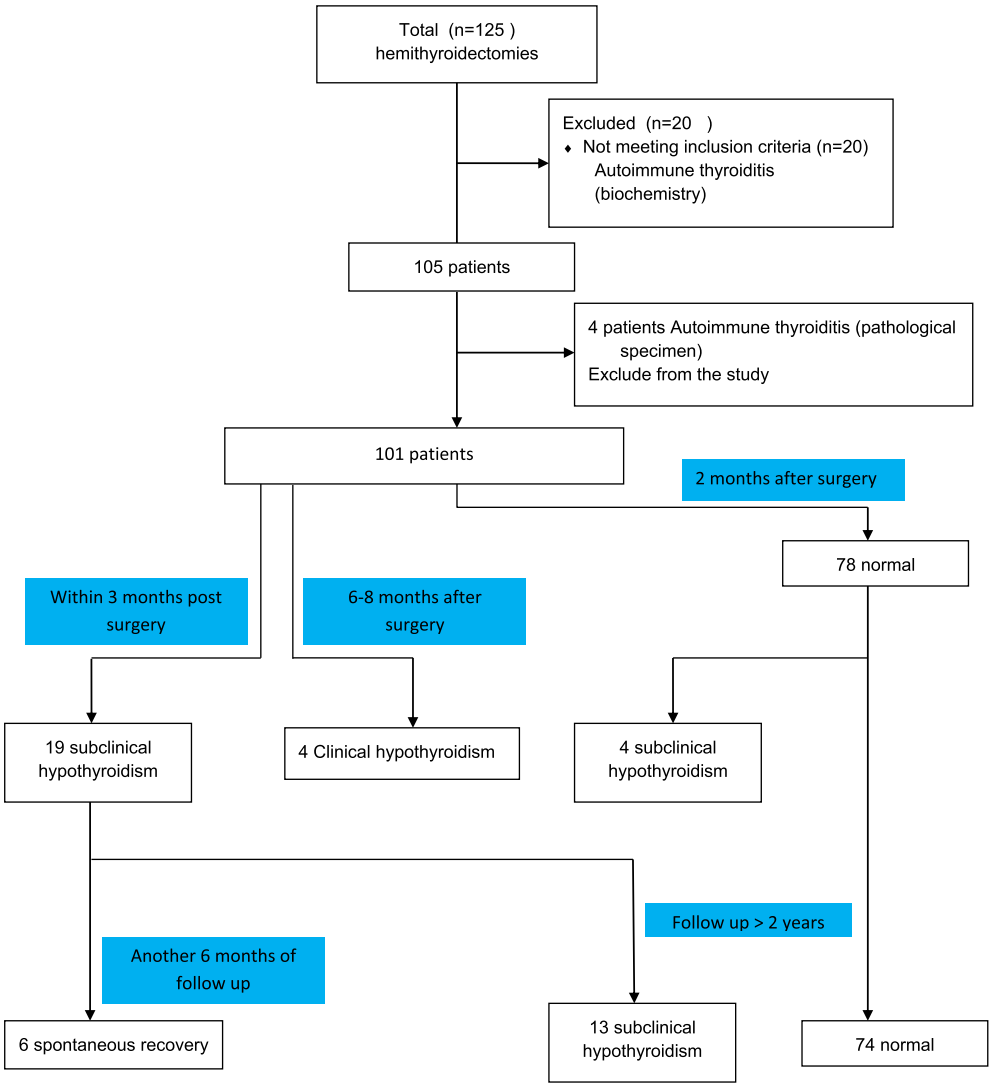

Figure 1 Flow chart of patient enrolment, exclusion and results.

Table 2 Result summary.

Character	Euthyroid	Hypothyroidism	P value
pre-operative TSH			
<2.0 uIU/mL	66	7	<0.001
≥2.0 uIU/mL	12	16	(Chi square test)
Thyroid remnant (g)	2.28–37.9 (median 6.36)	2.20–18.1 (median 3.55)	0.928
weight index (g/kg)	0.146	0.089	(Mann–Whitney U test)

hemithyroidectomy. Moreover, we also had a patient of follicular carcinoma with the background of nodular goitre. Left hemithyroidectomy was done and she was euthyroid post-operatively. There were too few patients with occult malignancy developing hypothyroidism post-hemithyroidectomy, thus the number was not representative and insignificant statistically. The role of TSH suppression post hemithyroidectomy had not been established.[18,19] However, in patients with occult malignancy and post hemithyroidectomy hypothyroidism, levothyroxine should be given earlier to render the patient euthyroid, as well as for TSH suppression.

Many authors did not address the issue of temporary hypothyroidism with spontaneous recovery after hemithyroidectomy.[1,4,6] On the other hand, few had reported temporary hypothyroidism in 33.5%–67% of patients.[3,13,21] In our study, we encountered six patients (26.1%) who had spontaneously recovered from hypothyroidism later. The mean duration of recovery was 8.7 months, which was much earlier than other literature reckoning 12–18 months.[3,13]

Many hemithyroidectomy patients had not been followed up long enough, particularly those with benign goitre, and hence post-operative hypothyroidism was missed. From our data, the longest duration of developing hypothyroidism was eight months. Thus we suggested all patients should be at least follow up for one-year duration,[20] or long term if they developed hypothyroidism.

The presence of anti-thyroperoxidase (ATO) was the most well-studied risk factor.[1,3,4,6,7] The literature reviewed that hypothyroidism post hemithyroidectomy ranging from 38.9% to 59%[1,4,6,7,22,23] Lymphocytic infiltration of the gland as seen in lymphocytic thyroiditis or Hashimoto's thyroiditis had a higher incidence for hypothyroidism.[4] Histology grading of the lymphocytic infiltration further defined the risk, with 49% for high grade compared to 10% for low grade.[1,] In our context, we had excluded those with ATO positive in order not to study this factor in depth. However, we encountered 24 patients with autoimmune thyroid diseases. Among the 24 patients of autoimmune thyroiditis, 15 were euthyroid after hemithyroidectomy (62.5%), 11 developed hypothyroidism (37.5%). Two out of the 11 patients of hypothyroidism recovered spontaneously later.

Among those with histological finding of autoimmune thyroid disease, there was a patient whose pre-operative ATO negative, develops hypothyroidism one year post hemithyroidectomy. She had been prescribed levothyroxine. There were literature reviewing that in those with ATO positive and autoimmune thyroiditis, the follow up duration should be minimally two years in order not to missed the delayed onset hypothyroidism.[3,4]

5. Conclusion

Hypothyroidism following hemithyroidectomy is not an uncommon condition. It happens one in five patients (20.8%, or 21 of 101 patients). The treatment is simple with oral levothyroxine. Generally, minimum of one year follow up is required in order not to miss those developing hypothyroidism post-operatively. Annual follow up is also enable us to detect those with spontaneous recovery from temporary hypothyroidism, as they do not require life-long levothyroxine.

Conflict of interest statement

The author declared no conflict of interest with National Cheng Kung University Hospital, and also nothing else to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2019.01.015.

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