https://muthmj.mu.edu.iq

Muthanna Medical Journal
2021; **8**(1):44-53

http://dx.doi.org/10.52113/1/2410-4590/2021-44-53

The role of thyroid stimulating hormone in the timing of thyroxin supplement after thyroid operations

Basil Abdulrazzaq Saadallah Al-Khayyat[*1], Berq J. Hadi Al-Yasseri [2], Anmar Jumaa Ghali [3]

Abstract

Thyroid Stimulating Hormone (TSH) levels can be measured accurately down to a very low serum concentration with an immunoassay. When the serum TSH level is in the normal range, measuring the T3 and T4 levels is redundant. The objective of this study is to study the relation of TSH levels postoperatively in thyroid surgeries with the timing for thyroxin treatment as a supplemental and suppressive therapy. A prospective cohort study was done on 84 patients underwent thyroid operations in Al-Yarmouk Teaching Hospital from March 2010 through November 2012. Patients underwent different thyroid operations (lobectomy, subtotal thyroidectomy and total thyroidectomy) for different thyroid pathology. Later, they were followed up by TSH assay in periods of 2, 4, 6 and 12 months postoperatively. Variables were compared by using the analysis of variance, ANOVA test. P – values equal or less than 0.05 and 0.01 were considered to be statistically significant and highly significant, respectively. The mean age of patients was 43.30 ± 10.19 years. The females made the vast majority of study sample (85.7%). Patients were divided into six groups: simple colloid goiters (17 patients), multinodular goiters (32 patients), solitary thyroid nodules (11 patients), Hashimoto's thyroiditis (8 patients), Graves' disease (8 patients) and papillary and follicular carcinomas (8 patients). The study revealed that all patients with malignant thyroid nodules (i.e. those with total thyroidectomies) and the vast majority of patients with Hashimoto's thyroiditis were in definite need for thyroxin treatment post-operatively. Other patients were variable in their need and timing of treatment according to the histopathological results and the type of operations. In conclusion; measurement of TSH level postoperatively is a good indicator for need of thyroxin treatment and for dose adjustment with the help of pathological results and the type of surgery.

Keywords: Thyroid gland, postoperative TSH, Thyroxin

*Corresponding Author: dr_basil79@yahoo.com
[1]Al-Yarmook Teaching Hospital
[2]Al-Nahrain University/ College of Medicine
[3]Central Teaching Hospital of Children
Received April 30, 2021; revised July 22, 2021; accepted July 30, 2021; published August 14, 2021

Introduction

Thyroid stimulating hormone (TSH) is a glycoprotein molecule synthesized and secreted from thyrotrophs basophile cells of the anterior pituitary gland [1]. It mediates iodide trapping, secretion, and release of thyroid hormones, in addition to increasing the cellularity and vascularity of the thyroid gland. Its secretion is regulated via a negative feedback loop by thyroid hormones (T4 and T3) levels. Because the pituitary has the ability to convert T4 to T3, the latter is thought to be more important in this feedback

control [2]. TSH is now firmly established as the first-line thyroid function test to assess thyroid status for most clinical conditions. An abnormal TSH is the first abnormality to appear in majority of thyroid diseases, where other thyroid tests can be normal. Using TSH as a single criterion has been shown to accurately classify the thyroid state of a patient in over 95% of cases [3].

TSH alone can be used to assess thyroid status when the pituitary-thyroid axis is stable. Non-thyroid illness, pituitary disease and various drugs can all affect the axis and cause discrepancies between TSH levels, thyroid hormone levels and the clinical state. Glucocorticoids, dopamine and octreotide can all suppress TSH secretion [4, 5]. Multiple factors influence the calculation of the TSH upper reference including population demographics like sex, ethnicity, iodine intake, body mass index, smoking status and age, as well as the failure to exclude the presence of subclinical thyroid disease. The TSH reference interval also varies with age and stage of pregnancy [6].

There is a large variety of available tests of thyroid function. However, in a surgical setting the investigations requested should be the minimum necessary to reach a diagnosis and formulate a management plan. Only a small number of parameters should be measured as a routine, although this may require supplementation or the measurements may need to be repeated when inconclusive [2]. Giving these facts, it becomes important to investigate the role of TSH in the timing of thyroxin supplement after thyroid operations. Consequently, this study was conducted to examine the relation of TSH levels postoperatively with the timing for thyroxin treatment as a supplemental and suppressive therapy in a sample of patients admitted to Al-Yrmook teaching hospital.

Material and methods

This is a prospective cohort study conducted on 84 goiters' patients underwent thyroid operations for different pathology during the period from March 2010 through November 2012. These patients were collected randomly from Al-Yarmouk Teaching hospital. All patients were investigated for thyroid function test (TSH, T3 and T4) and sometimes thyroid antibodies for those suspected with Hashimoto's thyroiditis and Graves' disease. Most of patients also underwent ultrasonography and fine needle aspiration cytology (FNAC), in addition to routine investigations for preparation to surgery (blood biochemistry, renal function tests and liver function tests).

The types of the operations were designed according to the clinical presentations and results of preoperative investigations, taking into account specific indications for certain types of operations to some patients. For example, all patients with diagnosed malignant thyroid nodules (papillary carcinoma) or suspected malignant thyroid nodules (follicular adenoma by FNAC) were operated by total thyroidectomy, while the patients of solitary thyroid nodule were operated by lobectomy. Most patients with simple colloid goiter, Hashimoto's thyroiditis and multinodular goiter were operated with subtotal resection of the thyroid; while other patients of Graves' disease, Hashimoto's thyroiditis and simple colloid goiter were treated with total thyroidectomy.

Postoperatively, all patients were subjected to TSH measurements using Mini-Vidas automated immunoassay analyzer in intervals of 2, 4, 6, 12 months and thyroxin treatment was given accordingly. During the follow up periods thyroxin was given to any patient with TSH value above 5 µIU/ml (normally

according to Mini Vidas standards, normal TSH is between 0.25-5 µIU/ml) with a beginning dose of 50 micrograms then on the follow up periods the doses were increased or decreased or stopped accordingly. In patients who were diagnosed to have papillary or follicular carcinoma, thyroxin (50 microgram) were given in a single dose daily within 2 weeks after the surgery and then followed up serially at same intervals with other patients and the dose of thyroxin adjusted accordingly to keep TSH below 0.1 µIU/ml (negligible) to prevent recurrence.

Statistical Analysis

The SPSS software program, version 20, was used for all computerized statistical analyses. The results were expressed as frequency & percentage or mean ± slandered deviation (SD). Variables were compared by using the analysis of variance, ANOVA test. *P* - values equal or less than 0.05 and 0.01 were considered to be statistically significant and highly significant, respectively.

Result

As mentioned previously, this study involved 84 goiters' patients. Their ages were ranged between 22 to 66-year-old with a mean of 43.30 ± 10.19 years. The females made the vast majority of study sample (85.7%). Regarding histopathological characteristics of patients, they were divided into six pathological groups: multinodular goiter 32 (38.1%), simple colloid goiter 17 (20.3%), solitary thyroid nodule 11 (13.1%), Hashimoto's thyroiditis 8 (9.5%), Graves' disease 8 (9.5%) and malignant thyroid nodules (papillary and follicular carcinomas) 8 (9.5%) patients. This classification was based on results of histopathological examination of postoperative excised specimens. The subtotal resection of the thyroid gland was performed in approximately two-thirds of operations (63.1%), while total thyroidectomy was done in nearly quarter of cases (23.8%); and the lobectomy was conducted for the remaining (13.1%). The clinic-demographic characteristics of the study design can be visualized in Table1.

Postoperative TSH results and follow-up

In the majority of patients, Thyroxin did not be given in the immediate postoperative period. However, in all patients with malignancies and in patients with benign goiters treated by total thyroidectomy which were 20 (23.8%), thyroxin was given immediately within the first 2 weeks after the operations. This action was done to replace the lost thyroid gland secretions, and to suppress the TSH to below 0.1 µIU/ml in those with malignant thyroid nodules. The follow-up measurements of TSH in these groups was done in the same time intervals as with other patients with suitable adjustment of TSH levels.

After two months, 58.3% of all patients didn't need thyroxin treatment, while 17.9% needed treatment of 50 micrograms and 23.8% needed a dose of 100-150 microgram of thyroxin. After four months of the operation, 53.6% of patients didn't need treatment, while 11.9% of patients needed thyroxin therapy of a dose of 50 micrograms and 34.5% of patients needed treatment of 100-150 microgram. Later on after six months of operations, those who didn't need treatment were in the same level as after four months (53.6%), while 9.5% of patients needed 50 microgram of thyroxin and 36.9% of patients needed 100-150 microgram of thyroxin. Finally, after one year from operation, a little increment in those patients who didn't need treatment was observed (54.8%), while those who need small dose of thyroxin (50 microgram) continue in decrement in comparison with the previous follow up periods and made about

7.1% of all patients, while those who needed higher doses (100-150 microgram) continue to increase in comparison with previous follow-up periods to become 38.1% of all patients. The follow up of these groups of patients and their thyroxin need are summarized in Figure1.

Table1.

Clinico-demographic characteristics of study sample

Variables		Frequency	Percentage
Sex	Female	72	85.7%
	Male	12	14.3%
Age Groups	< 30 year	4	4.8%
	30–39 year	24	28.6%
	40-49 year	30	35.7%
	50-59 year	22	26.1%
	≥60 year	4	4.8%
Histopathological studies	Multinodular goiter	32	38.1%
	Simple colloid goiter	17	20.3%
	Solitary thyroid nodule	11	13.1%
	Hashimoto's thyroiditis	8	9.5%
	Graves' disease	8	9.5%
	Papillary carcinoma	6	7.1%
	Follicular carcinomas	2	2.4%
Types of thyroid operations	Subtotal resection	53	63.1%
	Total thyroidectomy	20	23.8%
	Lobectomy	11	13.1%
Total		84	100%

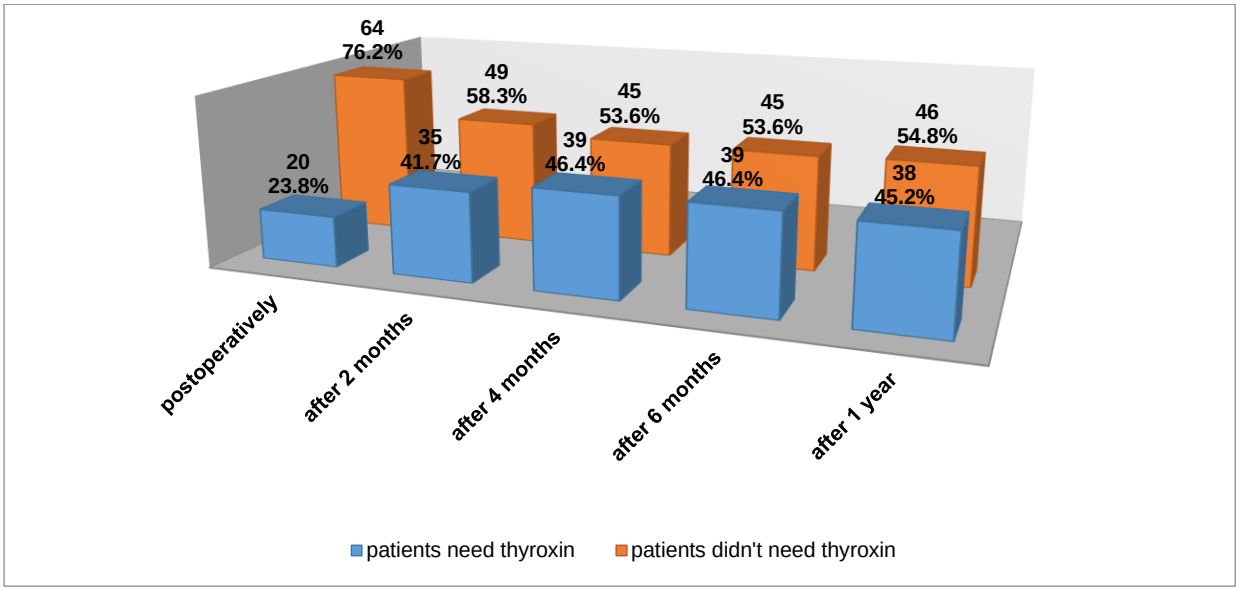

Figure1.

The need for postoperative thyroxin treatment during follow-up for the study participants

The mean TSH level for all patients (treated and not treated with thyroxin) was changed from 3.51 ± 2.87 µIU/ml after two months from the operations to a mean value of 1.81 ± 0.88 µIU/ml after one year from the operations. while the mean TSH for only the treated patients was changed from 5.93 ± 2.98 µIU/ml after two months from the operation to a mean value of 1.75 ± 0.93 µIU/ml after one year from the operation. The *p*-value for this change in TSH values in both situations was 0.0001 which is highly significant. This change in the mean value of the TSH for all patients and for those patients who are treated with thyroxin are summarized in Table 2.

Table 2.

Mean TSH change during follow-up measurements of patients

Time after operation	**Mean TSH level (in µIU/ml)**	
	For patients treated with thyroxin only	For all patients in the study
2 months	5.93±2.98	3.51±2.87
4 months	3.62±2.60	2.72±2.06
6 months	2.05±1.56	1.93±1.17
12 months	1.75±0.93	1.81±0.88
***P*-Value**	**0.0001**	**0.0001**

In those with simple colloid goiter (17 patients), 3 (17.6%) patients took thyroxin within 2 weeks postoperatively (in which total thyroidectomy was done), while 5 (29.4%) patients needed treatment after 2 months from the operations, and 6 (35.3) patients needed treatment after one year from the

operations. In patients with solitary thyroid nodule, no one from the whole 11 needed treatments after 2 months from the operations, and just 1 (9.1%) patient needed treatment after 4 months from the operation and continued till one year after the operation. With regard to multinodular goiter, no patient from the whole 32 patients needed treatment postoperatively and 8 (25%) of them needed therapy after 2 months from the operations, while 10 (31.2%) patients of them needed treatment after one year.

In Hashimoto's thyroiditis (8 patients), 3 (37.5%) patients took thyroxin within 2 weeks postoperatively (in which total thyroidectomy was done), while 7 (87.5%) patients needed treatment after two months from the operations, and 6 (75%) patients remained on thyroxin after one year. For those with Graves' disease (8 patients), 6 (75%) of them took thyroxin within 2 weeks postoperatively (in which total thyroidectomy was done), while 7 (87.5%) patients needed therapy with thyroxin in first two months after the operations according to TSH follow up and the same number (7 patients) continued in thyroxin need 1 year after the operations.

Concerning malignant thyroid nodules (papillary and follicular carcinoma), all 8 (100%) patients were given thyroxin within 2 weeks of the operations and just adjustment of the dose was done in the following follow up periods to keep TSH level below 0.1 µIU/ml. The need for thyroxin treatment in all studied patients according to their histopathological diagnoses depending on TSH measurements postoperatively till one year is summarized in Table3.

Table 4.

Relationship between thyroxin need in different histopathological cases and the time after operation according to TSH levels

Histopathological Type of Cases	**Number (%) of cases which needed thyroxin therapy**				
	Postoperatively in 2 weeks	**After 2 months**	**After 4 months**	**After 6 months**	**After 12 months**
Multinodular goiter	0 (0%)	8 (25%)	10 (31.2%)	10 (31.2%)	10 (31.2%)
Simple colloid goiter	3 (17.6%)	5 (29.4%)	5 (29.4%)	6 (35.3%)	6 (35.3)
Solitary thyroid nodule	0 (0%)	0 (0%)	1 (9.1%)	1 (9.1%)	1 (9.1%)
Hashimoto's thyroiditis	3 (37.5%)	7 (87.5%)	7 (87.5%)	6 75.0%	6 75.0%
Graves' disease	6 (75.0%)	7 (87.5%)	8 (100.0%)	8 (100.0%)	7 (87.5%)
Papillary carcinoma	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)
Follicular carcinomas	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)
Total	**20 (23.8%)**	**35 (41.7%)**	**39 (46.4%)**	**39 (46.4%)**	**38 (45.2%)**

Discussion

The TSH level serves as an endogenous indicator of the biologically active free T4 fraction and, as a result, is currently the best indicator of the thyroid function of an individual. In addition, the TSH level has other advantages over free T4 estimates in confirming the presence of thyroid diseases. First, each individual has his or her own free T4-TSH set point, where by any deviation from this genetically determined relationship changes the serum TSH level. Second, owing to the local nature of the T4 feedback at the pituitary gland, these alterations in serum TSH value amplify small changes in the circulating free T4 [7]. The net result of these unique attributes of measuring TSH is the ability to use it to detect thyroid dysfunction early in the course of thyroid disease.

Age and sex distribution of the study sample

The higher frequency of thyroid problems in female patients in current study may be attributed to stress related to multiple pregnancies and lactation and possibly the dietary iodine deficiency which is the case in many countries among which is Iraq [8]. Khan *et al* reported that Asian women had more economic and domestic responsibilities than men. They also reported greater frequency of thyroid problems in females than males [9].

Regarding age distribution in our study, the mean age of the affected individuals in the study was 43.30 ± 10.19 years, with the largest affected age group being in the fifth decade of life. Khan *et al* reported increased frequencies of thyroid problems with age. They have suggested that gradual increase in autonomous tissues with age making individuals more susceptible to thyroid problems [9]. In a survey conducted by Saima *et al*, the prevalence of goiter in the elderly population in a mildly to moderately iodine deficient area was 74% in patients aged 55-75 years and 54% in patients aged 76-84 years [10].

Type of operation

During the last decade there was a change in the behavior of surgery towards more radical surgery as near-total thyroidectomy or total thyroidectomy especially for Multinodular goiter (MNG). It was found that total thyroidectomy and near-total thyroidectomy are safe and effective approach in these conditions and in thyroid carcinoma [8]. Due to the changes of the pathology of thyroid gland, and the change in the behavior of surgeons all over the world toward more radical surgery, there was a real change in the extent of surgical excision of the gland. In fact, the increasing use of total thyroidectomy in Iraq has followed the changing practice in the Western countries. However, this change does not seem to be associated with rise in the complications [8].

Post-operative TSH results and follow-up

Regarding simple colloid goiter (17 patients), if we exclude the 3 patients who underwent total thyroidectomy postoperatively, so the total number of patients needed thyroxin whom had subtotal thyroidectomy from all patients of simple colloid whom operated by subtotal thyroidectomy will be 3 of 14 patients. These results are compatible with a study done by Gangi S *et al* which stated that hormone replacement therapy is unnecessary in most patients with simple colloid goiters operated by subtotal thyroidectomy since the majority of patients acquired euthyroid values a few months after operation [11].

In solitary thyroid nodule (11 patients), only one (9.1%) patient needed thyroxin supplements after the operations which were lobectomy which was done for all patients. In a study hold by Samantha J. Stoll et al for the incidence for hypothyroidism after lobectomy, they found a rate of 14.3% but they included some risk factors for hypothyroidism after lobectomy which are high TSH preoperatively, lower T4 level preoperatively, and Hashimoto's thyroiditis [12]. De Carlucci D. et al found a higher rate of hypothyroidism after lobectomy which reached 32.8% but they also found several risk factors predicting the occurrence of hypothyroidism after lobectomy which are patients with elevated preoperative TSH and postoperative thyroperoxidase antibody levels [13].

For those with multinodular goiter in our study, there were 8 (25%) patients who needed treatment 2 months postoperatively and 10(31.2%) patients needed thyroxin after 1 year from the operations. Kulaçoglu *et al* recommended early administration of thyroxin for patients with multinodular goiters treated by subtotal thyroidectomy to normalize TSH and to decrease recurrence rate [14].

The number of patients with Hashimoto's thyroiditis in current study was 8. Overall, 7 (87.5%) of them needed treatment after two months from the operations and 6 (75%) patients remained on thyroxin after one year. Thus, it is obvious that even with the exclusion of the three cases with total thyroidectomies, the majority of patients (3 out of 5 patients who underwent subtotal thyroidectomy) will need thyroxin treatment after 1 year from the operations according to the TSH follow up, and the total number needed thyroxin supplement was 6 out of 8 patients. Samuel F. *et al* had similar findings in that they stated that an incidence of hypothyroidism after subtotal thyroidectomy was 70% after 1 year [15].

For our cases with Graves' disease (8 patients), 6 (75%) patients took thyroxin within 2 weeks postoperatively (in which total thyroidectomy was done), while 7 (87.5%) patients needed therapy with thyroxin in first two months after the operations according to the TSH follow up and the same patients continued to need thyroxin 1 year after the operations. In current study the majority of patients whom suspected to have Graves' disease were treated by total thyroidectomy because this type of operation was recommended according to the national S2-guideline [16]. For the two patients of Graves' diseases whom were treated by subtotal resection, one of them (50%) needed thyroxin supplement after 2 months and continued in need after one year from the operations. In a study done by Kuma *et al* which included 67 patients whom had subtotal thyroidectomy for Graves' disease and did not receive any medical treatment for 8 to 12 years after surgery, they concluded that there is a large fluctuation in TSH levels of these patients postoperatively [17].

Different studies showed different results of post-subtotal thyroidectomy hypothyroidism in Graves' disease. A study holds by Limonard *et al* called concluded that the majority of patients with Graves' disease (83.9%) developed thyroid hormone deficiency after subtotal thyroidectomy. In addition, hyperthyroidism persisted or recurred in almost 10% of patients with Graves' disease after subtotal thyroidectomy, whereas euthyroidism was established in only 6.5% of patients [18]. Miccoli *et al* has other results and he reported a rate of 46.3% of hypothyroidism in their study which included 80 Patients [19]. Finally, Chi *et al* reported that the rate of hypothyroidism is as low as 21.1% in their study which included 166 patients [20].

We had 8 patients with malignant thyroid nodules in current study. All of them had total thyroidectomy as the treatment of choice for all diagnosed (papillary) and suspected (follicular) carcinomas. Orlo H. Clark suggested that total thyroidectomy is the treatment of choice for patients with thyroid cancer because residual cancer would persist in the remaining thyroid tissue in at least 61% of patients if only lobectomy had been performed [21]. Julie A. and Robert U published an article in the journal of surgical oncology in 2006 which stated that total or near-total thyroidectomy followed by I^{131} ablation and thyroid hormone suppression are most appropriate for the majority of patients with differentiated thyroid cancer, as retrospective analyses have shown that they reduce the risk of cancer recurrence, address the chance of multifocal intrathyroidal cancer, and facilitate the use of surveillance scans and thyroglobulin monitoring for postoperative recurrence [22].

Conclusion

Measurement of TSH level postoperatively is a good indicator for need of thyroxin treatment and for dose adjustment with the help of pathological results and the type of surgery. This study revealed there is a good relationship between the serum level of TSH after thyroid operations, the type of pathology and operative procedure. In that way in patients with thyroid carcinoma, Hashimoto's thyroiditis and Graves' disease initial thyroxin treatment is mandatory. In other pathological disorders operated with subtotal thyroidectomy, monitoring with TSH level should be done and the treatment is given accordingly.

The majority of patients with simple colloid goiter, solitary thyroid nodule and multinodular goiter who underwent subtotal resections didn't need thyroxin supplements postoperatively and only should be monitored with TSH follow-up. Most patients with Graves' disease needed thyroxin treatment postoperatively if total thyroidectomy was done. All patients with malignant thyroid nodules (papillary and follicular carcinomas) and the vast majority of patients with Hashimoto's thyroiditis will need lifelong thyroxin treatment with TSH follow up for dose adjustments postoperatively.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Mariusz W, Valerie F, Catherine R, et al. Thyroid-Stimulating Hormone and Thyroid-Stimulating Hormone Receptor Structure-Function Relationships. American Physiological Sociaty 2002;82(2):473-502.
2. Bouknight A. Thyroid physiology and thyroid function testing. Otolaryngolgy Clinic of North America 2003;36(1):9-15.
3. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. UK guidelines for the use of thyroid function tests; 2006.
4. Soh SB, Aw TC. Laboratory Testing in Thyroid Conditions - Pitfalls and Clinical Utility. Ann Lab Med. 2019;39(1): 3–14.
5. El Houssaine M, Bouamra O. Abnormal thyroid function and risk factor of gestational diabetes mellitus: a systematic review and meta-analysis. American Journal of BioMedicine 2017;5(2):86-98.

6. Ross DS, Burch HB, David S, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10): 1344-1420.
7. LoPresti JS. Laboratory tests for thyroid disorders. Otolaryngol Clin North Am. 1996;29(4):557-75.
8. Sulaiman TI, Al-Sarraf SA, Al-Rrawak K. Changing Patterns of Thyroid Pathology and Trends of Surgical Treatment. Baghdad medical college 2009;51(1):12-6.
9. Khan N, Shahmim A, Alam K, et al. Changing Patterns of Thyroid Pathology and Trends of Surgical Treatment. J.Fac.Med Baghdad. 2001;1(6): 400-403.
10. Saima S., Jerome M. and David G. Thyroid Nodules and Cancer in the Elderly. ENDOTEXT; 4 June 2012.
11. Gangi S, Prosperini U, Costanzo M. et al. The usefulness of thyroxine treatment after subtotal thyroidectomy for endemic goiter. Minerva Chir. 1994;49(1-2):51-3.
12. Samantha J, Susan C, Jing L, et al. Thyroid hormone replacement after thyroid lobectomy. Surgery. 2009;146(4):554-8.
13. De Carlucci D, Tavares M, Obara M, et al. Thyroid function after unilateral total lobectomy: risk factors for postoperative hypothyroidism. Arch Otolaryngology Head and Neck Surgery; 2008;134(10):1076-9.
14. Kulaçoglu H, Dener C, Ziraman I, et al. Thyroxin prophylaxis after bilateral subtotal thyroidectomy for multinodular goiter. Endocr J. 2000;47(3):349-52.
15. Samuel F, William A. Struma Lymphomatosa (Hashimoto's Disease). Annals of Surgery. 2000;141(5):737-746.
16. Katja M, Katja S, Dirk L, et al. Total versus near-total thyroidectomy in Graves' disease and their outcome on postoperative transient hypoparathyroidism. Biomed Central; 2012;13:234.
17. Kuma K, Matsuzuka K, Kobayashi A, et al. Natural course of Graves' disease after subtotal thyroidectomy and management of patients with postoperative thyroid dysfunction. Am J Med Sci. 1991;302(1):8-12.
18. Limonard EJ, Bisschop PH, Fliers E, et al. Thyroid function after subtotal thyroidectomy in patients with Graves' hyperthyroidism. Scientific World Journal. 2012;2012:548796.
19. Miccoli P, Vitti P, Rago T, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery. 1996;120(6):1020–25.
20. Chi SY, Hsei KC, Sheen-Chen SM, et al. A prospective randomized comparison of bilateral subtotal thyroidectomy versus unilateral total and contralateral subtotal thyroidectomy for Graves' disease. World Journal of Surgery. 2005;29(2):160–63.
21. Clark OH. Total thyroidectomy: the treatment of choice for patients with differentiated thyroid cancer. Ann Surg. 1982;196(3): 361–370.
22. Julie A, Robert U. Total thyroidectomy for differentiated thyroid cancer. Journal of Surgical Oncology. 2006;94(8): 701–7.