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Study of the Effects of Postoperative Levothyroxine Dosage in Patients Undergoing Thyroidectomy: Combined Analysis of Retrospective and Prospective Cohort Study

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ABSTRACT

Background: The conventional standard treatment approach for thyroid cancer has been complete thyroidectomy with or without radioactive iodine (RAI) ablation, followed by thyrotropin suppression. Levothyroxine has been advocated for TSH suppression to prolong survival and decrease tumor recurrence, particularly in high-risk patients.

Objective: This study was aimed to compare the effect of high dose (ablative dose) and low dose (therapeutic dose) of levothyroxine on bone density, calcium levels and Vitamin D levels.

Patients and Methods: This retrospective and prospective cohort study included a total of 100 patients presented with thyroid disorders, attending at Department of the General Surgery and Out-Patient Clinic of Endocrine Surgery Unit, Mansoura University Hospitals. This study was conducted between November 2020 and the end of April 2022.

Results: The post thyroidectomy levothyroxine dosage had statistically significant effect on results on bone mineral density especially in ablative dose of levothyroxine which has osteoporotic effect. There was no significant difference between calcium levels and Vitamin D levels preoperatively between therapeutic and ablative dose while there was correction of calcium levels and vitamin D levels post operatively in therapeutic dose while in ablative dose there was a decrease in average results of serum calcium and vitamin D levels after 6 months.

Conclusion: It could be concluded that the high dose of levothyroxine which is considered as ablative dose of post thyroidectomy hypothyroidism due to differentiated thyroid cancer have adverse effects on metabolic profile regarding calcium and 25 hydroxyl vitamin D which may carry hazards of bone mineral density regarding osteopenia and osteoporosis.

Keywords: Poorly Differentiated Thyroid Cancer, Thyroidectomy, thyroid stimulating hormone, hyperthyroidism, Levothyroxine, Ablative Dosage, Bone Mineral Density,

INTRODUCTION

Thyroidectomy is one of the most common elective surgical procedures in the world needed for various thyroid disorders. Total thyroidectomy or Near Total thyroidectomy or hemithyroidectomy has been accepted as the current surgical therapy for benign and malignant thyroid disorders, but extensive resection might increase the risk of post-operative complications **(1).** Post thyroidectomies the patients may need replacement therapy according to the function or the remaining part of the thyroid gland or either total replacement or ablative therapy in other conditions **(2).**

It was discovered that the old standard therapy approach for differentiated thyroid cancer involves complete thyroidectomy, followed by RAI ablation and subsequently thyrotropin (i.e., thyroid stimulating hormone [TSH]) suppression. The greatest method for avoiding tumor recurrence and increasing survival rate, particularly in high-risk patients, is TSH suppression with levothyroxine **(3).**

It is understood that long-term administration of high doses of levothyroxine may have a negative impact on bone health. Endogenous hyperthyroidism is known to increase the risk of osteoporosis and osteoporotic fractures, even at a preclinical level **(4)**.

Numerous observational studies have noted changes in the indicators of bone turnover or bone mineral density, particularly in postmenopausal women. Additionally, small-scale randomized controlled research revealed that TSH suppression increased the chance of being diagnosed with osteoporosis postoperatively **(5).**

This study was done to compare the effect of high dose (ablative dose) and low dose (therapeutic dose) of levothyroxine on bone density, calcium levels and Vitamin D levels.

PATIENTS AND METHODS

This retrospective and prospective cohort study included a total of 100 patients presented with thyroid disorders, attending at Department of the General Surgery and Out-Patient Clinic of Endocrine Surgery Unit, Mansoura University Hospitals. This study was conducted between November 2020 and the end of April 2022.

The patients underwent total thyroidectomy and final pathology was done then the patients were divided into two groups; **Group 1 (benign group)** consisted of 51 patients, received therapeutic dose of levothyroxine to reach the target average levels of TSH. **Group 2 (Malignant)** consisted of 49 patients received ablative dose of levothyroxine to reach target suppressive levels of TSH. The replacement doses according to body

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weight were the therapeutic dose: 1.6 mg\kg, The ablative dose: 3.2 mg\kg.

Inclusion criteria:

Patients ≥ 18 years with normal thyroid function and were fit for surgery. **Exclusion criteria:** patients with history of any thyroid surgery, diabetic patients, patients with chronic kidney diseases, patients with chronic liver diseases, patients with autoimmune diseases, patients with parathyroid abnormalities and pregnant patients.

All patients underwent full medical history taking, general and local examination, radiological investigations, full Laboratory investigations and indirect laryngoscope. The history included personal history, complain, present history, past medical history, previous medication, and family history.

The clinical examination included general body examination and local examination, All clinical findings were documented for site of the lesion related to other structure, size of the lesion either big or small, shape either consistent with thyroid enlargement or lymph node or any other swelling, consistency of the swelling or lesion either soft or hard to give rough idea about the lesion, mobile or fixed, relation to surroundings structures, skin covering the lesion fixed to it or freely mobile, if there is extension retrosternally, pulsation if there is toxic goiter as well as audible bruit.) And lymph nodes of neck were assessed if there was abnormal increase in size or painful examination.

Routine laboratory investigations included complete blood count, bleeding time & clotting time, renal and liver function tests, serum calcium (total and ionized) preoperative and post-operative, vit D levels, preoperative and post-operative and thyroid function tests: T3, T4, TSH, free T3 & T4. Radiological studies included thyroid ultrasound, X-ray neck and upper chest, CT scan for selected patients and DXA scan were done.

DEXA scan

The DXA test was done with a Xray machine which has an extension over the table that you lay on. Patients comfortably enjoy the test without feeling claustrophobic as its open machine. The machine sent a low x-ray beam that set two compositions within your body, soft tissue was calculated by one and the bone was calculated by the other beam [(6)].

Postoperative Follow Up

One month, 3 months and 6 months postoperative: ultra- sensitive TSH, serum calcium and vitamin D were estimated, and replacement (either therapeutic or ablative) dose of levothyroxine was given accordingly. DXA scan was done 6 months postoperative.

Ethical consideration:

This study was ethically approved by institutional review board (IRB) at Mansoura University. Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical Analysis

All data were collected in a performed sheet then entered into an electronic spreadsheet (Microsoft Excel) and transferred into Statistical Package for Social Sciences (SPSS). Data analysis was performed SPSS software, version 18 (SPSS Inc., PASW statistics for windows version 18. Chicago: SPSS Inc.), analyzing qualitative data using number and percent, while quantitative data was analyzed using median (interquartile range) for unusual, distributed data and mean standard deviation for normal distributed data, that was used following normally testing by Kolmogrov-Smirnov test. After that testing the obtained results at (0.05) level. Chi-square and Fischer exact tests were used to compare qualitative data between groups as appropriate. student T test and Mann Whitney U test were used to compare between 2 studied groups for normally and un-normally distributed data, respectively paired T-test and Wilcoxon signed rank test were used to compare between 2 studied periods for normally and unmorally distributed data.

RESULTS

In this study, there were 51 patients had benign thyroid lesion and 49 patients had Malignant thyroid lesion. There were no statistically significant differences among both groups regarding age, sex, weight, height, BMI, history of smoking ($P>0.05$). There were statistically significant differences among both groups regarding history of fractures, parental history of fractures ($P<0.05$) (table 1).

Table (1): Sociodemographic characteristics distribution according to pathology of the studied cases

	Benign (N=51)	Malignant (N=49)	Test of significance
Age/years (Mean±SD)	43.51±10.86	42.64±11.51	t=0.392 (p=0.696)
Sex Female Male	 43(78.2) 12(21.8)	 32(71.1) 13(28.9)	 χ^2=0.660 p=0.417
Smoking Smoker Non Smoker	 14(25.5) 41(74.5)	 11(24.4) 34(75.6)	 χ^2=0.013 p=0.908
History of fractures	4(7.3)	24(53.3)	χ^2=26.05, p<0.001*
Parental history of fractures	1(1.8)	9(20.0)	χ^2=9.09, p=0.003*
Weight/Kg (Mean±SD)	73.09±10.59	76.13±10.27	t=1.45, p=0.151
Height/cm (Mean±SD)	161.49±6.28	162.89±6.72	t=1.07, p=0.286
BMI(Kg/m^2) (Mean±SD)	28.13±4.44	28.84±4.51	t=0.780, p=0.437

χ^2=Chi-Square test, t: Student t test

There was no statistically significant difference among both groups regarding preoperative average of TSH level. While the average TSH level 3 months postoperatively was statistically significant different among both groups. Also, the average TSH level 6 months postoperatively was statistically significant different among them (P<0.05). So, the patients with benign lesions had TSH levels within normal levels 3- and 6-months postoperative while patients with Malignant lesion showed lesser TSH levels 3- and 6-months postoperative (Table 2).

There was no statistically significant difference among both groups regarding preoperative average of Ca^{++} level. While the average Ca^{++} level 3 months postoperatively was statistically significant different among them (P<0.05), also, the average Ca^{++} level 6 months postoperatively was statistically significant different among them (P<0.05). So, the patients with benign lesions had more Ca++ levels within levels 3- and 6-months postoperative than the patients with Malignant lesion within 3- and 6-months postoperative (Table 2).

There was no statistically significant difference among both groups regarding preoperative average of vitamin D level. While the average Vitamin D level 3 months postoperatively was statistically significant different among them (P<0.05). Also, the average Vitamin D level 6 months postoperatively was statistically significant different between them (P<0.05). So, the patients with benign lesions had more Vitamin D levels within levels 3- and 6-months postoperative than the patients with Malignant lesion within 3- and 6-months postoperative (Table 2).

Table (2): Comparison of TSH, calcium and vitamin D pre and post-operative value between benign and malignant lesions.

		Benign n=51	Malignant n=49	Test of significance
TSH (uIU/mL)	**TSH pre**	1.44(1.0-2.7)	1.4(0.8-2.15)	z=0.738, p=0.460
	TSH after 3 months	3.7(2.7-5.4)	0.12(0.075-1.40)	z=7.16, p<0.001*
	TSH after 6 months	3.20(2.3-4.2)	0.18(0.05-1.70)	z=6.78, p<0.001*
Ca^{++} (mg/dL)	**Ca^{++} pre**	8.81±1.04	8.62±0.71	t=1.03, p=0.307
	Ca after 3 months	8.79±0.56	8.46±0.61	t=2.78 p=0.007*
	Ca after 6 months	8.81±0.41	8.21±0.57	t=6.20 p<0.001*
Vitamin D (IU)	**Vitamin D pre**	21(19-25)	23(18.5-27.75)	z=1.59 p=0.112
	Vitamin D after 3 months	29(26-32)	24(17.5-28)	z=4.49 p<0.001*
	Vitamin D after 6 months	36(31-38)	21(13.5-32)	z=5.65 p<0.001*

Non-Parameters described as median (Interquartile range), Z: Mann Whitney U test. t: Student t test. *Statistically significant

The average spine T score, the average spine Z score, the average neck femur T score and the average neck femur Z Score showed no statistically significant difference between group of benign lesions and group of malginant lesion (table 3).

Table (3): Comparison of T & Z score spine and neck femur between benign and malignant lesions

	Benign n=51	Malignant n=49	test of significance
T score spine	0.2(-0.7, 0.65)	-0.4 (-1.8, 0.4)	z=0.992, p=0.321
Z score spine	-0.40(-1.1, 0.20)	-1.4(-2.7, 0.2)	z=1.23, p=0.218
T score neck femur	0.1(-0.85, 0.35)	0.0(-0.40, 0.50)	z=0.796, p=0.426
Z score neck femur	-0.20 (-0.90, 0.1)	-0.90(-1.1, 0.10)	z=0.914, p=0.361

Non-Parameters described as median (Interquartile range), Z:Mann Whitney U test *statistically significant

DISCUSSION

Thyroidectomy is a common elective surgical intervention in the world needed for various thyroid disorders. Total thyroidectomy or Near Total thyroidectomy or hemithyroidectomy has been accepted as a surgical therapy for benign and malignant thyroid disorders, but extensive resection might increase the risk of post-operative complications [(7)]. Post thyroidectomies, the patients may need replacement therapy according to the function or the remaining part of the thyroid gland or either total replacement or ablative therapy in other conditions (malignancies) [(2)].

Similar to osteoporosis, differentiated thyroid carcinoma is a common condition that primarily affects women. Lack of vitamin D is prevalent, especially among the elderly. Due to inadequate sun exposure, nutritional imbalances, and poor adherence to its therapeutic formulation, this result is exacerbated in those who are institutionalized or have other comorbidities [(8)].

The age-related depletion of vitamin D in our patients, like in the general population, might be the cause of the decline in vitamin D at the second examination in all subjects, despite treatment. The most frequent locations of osteoporotic fracture seen in the general population were where the fractures documented in both patient groups occurred. Additionally, a second examination of the fracture patients supported the predictive power of FRAX [(9)].

Total thyroidectomy and long-term TSH-suppressive therapy is the routine management for patients with differentiated thyroid carcinoma. However, the negative effects of prolonged maintenance of a suppressed TSH on bone quality and fracture risk is of much concern nowadays.

The point of comparison between the two groups included data collected from the patients showed the levels of serum TSH, total serum calcium, total vitamin D levels preoperatively, three and six months post operatively as well as DEXA scan results T score and Z score preoperative and 6 months' postoperative data

Our data showed that differentiated thyroid carcinoma incidence is predominant in middle aged female with average age 43 years with BMI 28 (kg/m^2) overweight mostly in non-smokers. Sciuto *et al.*, [(10)] showed that Median age at diagnosis was 46 years. Papillary cancer and low pathological tumor–node–metastasis stages represented >80% of cases.

Furthermore, comparing benign and malignant condition we found out that differentiated thyroid carcinoma is predominant in females than males average age 42 years old nonsmoking. while **Sciuto *et al.*** [(10)] showed the prevalence of DTC in females with mean age 40 in his study.

Considering TSH levels according to the pathology, we found that there was no significant change preoperatively between benign lesions and differentiated thyroid cancer. While 6 months postoperatively there was significant change in TSH levels in differentiated thyroid cancer while no significant change in benign lesions. Other study made by **Dorange *et al.*** [(11)] was in favor of our study showed that the differentiated thyroid cancer or some benign lesions doesn't affect TSH levels preoperatively or postoperatively. While **Haymart *et al.*** [(12)] showed that some types or differentiated thyroid cancer affect TSH levels.

In our study there was no significant difference between calcium levels preoperatively between benign and malignant group. However, there was significant change in calcium levels between pre-operative and post-operative state between benign and malignant conditions, as calcium levels were higher in benign conditions. Also, there was significant change in calcium levels in benign conditions in 6 months than in malignant conditions. Similarly in other study conducted by **Baltaci *et al.*,** [(13)] showed that changes in the serum and thyroid tissue levels of trace elements like calcium, zinc and selenium, which play a critical role in thyroid function, might be associated with the pathogenesis of thyroid cancer.

In this study, there was no significant difference between vitamin D levels preoperatively between benign group and malignant group. However, there was significant change in vitamin D levels between pre-operative and post-operatively in benign and malignant condition, as VIT D levels were higher in benign conditions than malignant lesions. Also, there was significant change in VIT D levels in malignant conditions in 6 months than 3 months than benign conditions As VIT D decreased in 6 months variation in malignancy while no significant change in benign lesions.

However, in other study conducted by **Sulibhavi *et al.*** [(14)] there was no significant change in VIT D levels in malignant or benign lesions as different racial subgroups had different rates of Vitamin D deficiency,

neither race nor socioeconomic status showed correlation with cancer stage.

While in study conducted by **Kim *et al.*** [15] there was significant change in VIT D levels in malignant condition. Which showed that Vitamin D deficiency is significantly associated with postoperative symptomatic hypocalcemia in thyroid cancer patients undergoing Total thyroidectomy plus Central compartmental node dissection.

In our study we conducted DEXA scan for the patients to determine the Bone density radiologically preoperatively and 6 months postoperatively and comparing our results with other studies and we found out that there was no significant difference between T score and Z score in spine between benign and malignant group. Regarding T score and Z score in neck femur between the benign and malignant group, there was no significant difference between them. which was similar to study done by **Lee *et al,*** [16] who showed that there was no significant relationship between suppressive dose and changes in Bone mineral density

So, in our study by interpreting DEXA scan results, we can find out that the dose of levothyroxine did not have any effect on bone density statistically while in some cases there were changes numerically.

CONCLUSION

Regarding the patients with thyroid cancer, we found that the post-thyroidectomy dose of the levothyroxine should be monitored routinely especially as they were exposed to ablative dose. Our study concluded that the high dose of levothyroxine which is considered as ablative dose of post thyroidectomy hypothyroidism due to differentiated thyroid cancer have negative effect on metabolic profile regarding calcium and 25 hydroxyl vitamin D which may carry hazards of Bone mineral density regarding osteopenia and osteoporosis.

RECOMMENDATIONS

we recommend strict follow up of patients with thyroid cancer after operation and supervise for replacement therapy regarding thyroxine, calcium, phosphorus and vitamin D assay and replacement.

Conflict of interest: The investigators declare no conflict of interest.

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