

PREVENTION OF RECURRENCE OF DIFFUSE AND NODULAR NONTOXIC GOITER WITH LIFETIME PHYSIOLOGIC LEVOTHYROXINE MAINTENANCE THERAPY

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ABSTRACT

Background and Objectives: Goitrous thyroid is due to a defective thyroid hormogenesis leading to a lifetime process of thyroid enlargement due to TSH stimulation. Twenty percent or less of diffuse goiter or solitary nodules will actually regress significantly as a result of levothyroxine (L-T4) treatment, and regrowth is seen after cessation of therapy. The aim of this study is to describe the importance of lifetime maintenance with levothyroxine in preventing goiter recurrence in diffuse and nodular non-toxic goiter.

Methods: This is a retrospective review of sixty patients (56 females, 4 males) on long-term levothyroxine treatment were analyzed (age range; 18 to 72 years). 46 patients had diffuse goiter and 14 patients had nodular goiter. Big nodules that were biopsied were negative for malignancy. Volumes were measured using ultrasound.

Results: Mean TSH at initial consult was 2.8 mIU/L +/- 6.7 (n=56). Thyroid ultrasound mean lobe size (n=43) were the following: right lobe = 4.85 X 1.66 cm and left lobe = 4.72 X 1.61 cm. Overall, initial daily levothyroxine dose given ranged between 25 to 200 mcg with a mean dose of 87.5 mcg +/- 17.7 and were subsequently maintained on 25 to 75 mcg with a mean daily dose of 68.75 +/- 25.9 mcg. For nodular goiters alone, initial and maintenance daily LT4 dose were 100 mcg and 56.25 mcg respectively. Whereas, for diffuse goiter, initial and maintenance daily LT4 dose were 75 mcg and 68.75 mcg respectively. Duration of follow-up was 3 months to 6 years. TSH level was statistically lower ($p < 0.05$) during maintenance therapy (1.02 mIU/L +/- 0.7 compared to 2.8 mIU/L +/- 6.7 at baseline) compared to initial therapy. Volume reduction was about 15% (n=26) and maintained thereafter.

Conclusion: Goiter is a lifetime disease. LT4

maintenance therapy to maintain a physiologic level of TSH (0.3 to 1.0 mIU/L) will prevent recurrence.

Keywords: diffuse goiter, nodular goiter, levothyroxine, prevention of recurrence

INTRODUCTION

Goitrous thyroid can be traced back to a defective thyroid hormogenesis leading to a lifetime process of thyroid enlargement due to TSH stimulation.¹ Goiter should thus be regarded as a complex trait in which both genetic susceptibility and environmental factors probably contribute to the development of disease.² It is generally accepted that iodine deficiency is a major environmental factor contributing to both endemic and sporadic simple goiter.³ In fact, thyroid size is negatively correlated to urinary iodine excretion.⁴ The prevalence of iodine deficiency in the Philippines is mild based on urinary excretion levels. However, some cases of severe and moderate IDD also exist among the children.⁵ Other factors, such as cigarette smoking, infections, drugs, and goitrogens, may play a role in the genesis of goitrous disease together with a genetic background of susceptibility. Constitutional factors such as gender are clearly implicated in the etiology, because the ratio of females to males in nonendemic goiter regions may exceed from 5:1 to 10:1.² However, the natural history with respect to growth and function varies and is difficult to predict in a given patient because no specific growth parameters exist. Therefore, it is difficult to decide whether an individual patient can be monitored without treatment or should have treatment before the goiter grows any further and possibly affects treatment outcome adversely.⁶

There are varying recommendations regarding the value of LT4 suppression therapy for solitary thyroid nodule and diffuse non-toxic goiter. This treatment is intended to shrink existing nodules, and to prevent the occurrence of new nodules.⁸ Twenty percent or less of solitary nodules will actually regress significantly as a result of L-T4 treatment, and regrowth is seen after cessation of therapy.^{9,10} Experts have advocated the role of continuous levothyroxine treatment with a dose of 2.2-2.5ug/kg until the desired nodule and goiter volume reduction is achieved,⁸ however, discontinuation of treatment led to a number of significant recurrence.⁴ Nodules

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grow less if serum TSH is suppressed below 0.1 mIU/L; however, osteoporosis is now a growing concern.¹¹ In a retrospective analysis among Filipino patients receiving thyroid hormone suppression therapy, osteoporosis (most prominent in the lumbar spine) was noted in 50% of cases. In the same study, patients receiving physiologic maintenance therapy had a lower incidence of osteoporosis (also noted at the lumbar spine) at 11.7%.¹¹ The aim of this study is to describe importance of long term or lifetime physiologic maintenance therapy with levothyroxine in preventing goiter growth and recurrence in diffuse or nodular non-toxic goiters.

MATERIALS AND METHODS

This is a descriptive and retrospective analysis of patients seen in University of Santo Tomas outpatient clinic between 1998 to 2005 who were maintained on long-term physiologic dose of levothyroxine of more than 6 months. Outpatient records were reviewed. Ninety-five patients' records were available for review however 35 patients were excluded due to the following factors: nine patients received previous radioactive iodine ablation, fifteen patients had previous thyroid surgery for benign adenomas¹⁰ and diffuse non-toxic goiter,⁵ five patients were pregnant during follow up visits, six patients had thyroid carcinoma by fine needle aspiration biopsy.

RESULTS

There were 60 patients seen in the Outpatient Endocrine Clinic who were included in the analysis. Fifty-six patients were female and 4 were male. Diffuse non-toxic goiter was present in 46 cases and nodular non-toxic goiter in 14 cases. Majority of patients were in their 3rd and 4th decade (age range: 18 to 72, mean 33.7 +/- 10.9 years). Nodules with size range of 1.5 to 2.5 cm in largest dimension were biopsied and were negative for malignancy. Fourteen patients seen were lost to follow-up after the first visit. TSH range at initial consult was between 0.31 to 18.0 with a mean value of 2.8 mIU/L +/- 6.7 (n=56) (see table I). FT4 range was between 3.4 to 29.0 pMol/L with a mean value of 15.0 pMol/L +/- 6.7 (n=46) (see table I). Palpation showed grade I to II goiter with mean size of the thyroid by ultrasound (n=43) as follows: right lobe: 4.85 X 1.66 and left lobe: 4.72 X 1.61 cm (see table I). Overall, initial daily LT4 dose given range from 25 to 200 ug per day with a mean dose of 87.5ug +/- 17.7 and were maintained on LT4 at 25 to 75 ug with a mean daily dose of 68.75 +/- 25.9 . For thyroid nodule, mean dose of LT4 was 100ug per day initially and mean daily maintenance dose was 56.25ug (see table II). For diffuse non-toxic goiter, mean dose of LT4 was 75ug initially and mean daily maintenance dose of 68.75ug (see

table II). Mean duration of follow-up was 18 +/- 14 months (range; 6 months to 20 months) for nodular non-toxic goiter (see table II) and 17 +/- 17 months (range; 6 months to 74 months) for diffuse non-toxic goiter (see table II). Thyroid function test on follow ups were as follows: TSH range of 0.3 to 3.39 with a mean value of 1.02 mIU/L +/- 0.7 (n=32), FT3 mean 0.8 to 1.3 with a mean value of 0.91pMol/L +/- 0.2 (n=10), FT4 5.5 to 47 pMol/L with a mean value of 26.72pMol/L +/-18.6 (n=31)(see table I). TSH was statistically lower ($p < 0.05$) after physiologic levothyroxine maintenance therapy (2.8 mIU/L +/- 6.7 vs. 1.02 mIU/L +/- 0.7). Volume reduction was about 15% (n=26) and clinically, thyroid gland size were maintained within normal thyroid limits.

Table I. Thyroid Function Tests and Ultrasound Measurements

	Baseline measurements	Follow-up
TSH (mIU/L) (n=56)	0.31 to 18.0 mean: 2.8 +/- 6.7	0.3 to 3.39 mean: 1.02 +/- 0.7
FT4(pMol/L) (n=46)	3.4 to 29.0 mean: 15.0 +/- 6.7	5.5 to 47 mean: 26.72 +/- 18.6
Ultrasound of the thyroid (mean size) n= 15	R: 4.85 X 1.66 cm L: 4.72 X 1.61 cm	R: 4.11 X 1.36 L: 4.14 X 1.35

Table II. Levothyroxine Dosage and Duration of Follow-Up in Both Diffuse and Nodular Non-Toxic Goiter

	Nodular non-toxic goiter	Diffuse non-toxic goiter
LT4 dosage	100ug mean: 56.25 ug	75 ug mean: 68.75 ug
Duration of follow-up	6 to 20 months mean: 18 months	6 to 74 months mean: 17 months

DISCUSSION

A. Dosage and duration of levothyroxine suppression therapy

The efficacy of levothyroxine therapy to reduce thyroid nodule size has been a matter of controversy for many years. Because of growing concern about potential adverse effects of long-term suppressive doses of levothyroxine on the cardiovascular and skeletal systems, no definite recommendation exists. Previous studies showed that among patients who received thyroid hormone suppression therapy, 0% to 14% of patients had nodules that grew more than 50%, whereas 14% to 22% of patients who did not receive therapy or placebo had nodules that grew

more than 50%. In a 5-year study by Papini, new nodule formation were noted in 28% of placebo vs. 7% in those maintained on levothyroxine.¹² In a recent meta-analysis of 6 randomized controlled trials comprising 346 patients, it was found that only 22% of patients treated with L-T4 compared with 10% in the control groups, had a nodule volume decrease by more than 50%. Overall treatment response did not achieve statistical significance but was associated with a trend toward a reduction of more than 50% in nodule volume after 6 to 12 months of L-T4 therapy.¹³ The lack of overlap between patients who did and did not receive thyroid hormone suppression therapy suggests that such therapy may prevent growth of existing benign thyroid nodules.⁽¹⁴⁾ This retrospective analysis demonstrated that long term treatment with levothyroxine in both nodular and diffuse goiters with the shortest duration of 17 months can adequately control the growth of these goiters and may even decrease their size from baseline. No significant adverse events noted. However, bone mineral density were not done in these patients and therefore the aspect of possible bone resorptive effects of long-term levothyroxine cannot be assessed. Parallel to the unestablished guideline regarding efficacy of longterm levothyroxine treatment, there is still no exact recommendation regarding levothyroxine dosage. Our data showed that levothyroxine dose between 25 to 200ug with a mean dose of 87.5 ug daily at 1st 6 months then maintained at a mean dose of 68.5 ug daily for another 12 months can cause at least 15% volume reduction in thyroid volume.

B. TSH suppression and effect on bone mineral density.

No definite recommendation exists regarding level of TSH suppression. In a review of published expert opinions, strong TSH suppression was a TSH of <0.1 mIU/L, moderate suppression was a TSH of 0.1 to 0.3, mild to moderate suppression was a TSH of 0.4 to 1.0. In a consensus of endocrinology practitioners from NIH, moderate suppression was a TSH of 0.1 to 0.4, mild suppression was a TSH of 0.4 to 1.0. Based on evidence grading, the evidence is strong for mild to moderate suppression and that is a TSH of <1.0 mIU/L.⁸ In our retrospective study, with a mean duration of 17 months on LT4 suppression treatment, TSH range on follow up analysis was at 0.3 to 3.39 mIU/L with a mean value of 1.02 mIU/L +/- 0.7. This resulted to a 15% reduction in thyroid volume with no increase in size of the previously noted thyroid nodules. No significant adverse events noted. However, bone mineral density were not done in these patients and therefore the aspect of possible bone resorptive effects of long-term levothyroxine cannot be assessed.

C. Our Recommendation. Although, this is a retrospective study and general recommendation based on these results cannot be formulated, it may still be reasonable to offer this option to carefully selected patients whose risk for development of potential adverse effects is low, and consider discontinuation of treatment if no objective response is seen after a year as assessed by palpation and objective measurement using ultrasonography.

In our study, levothyroxine dose between 25 to 200ug with a mean dose of 87.5 ug daily at 1st 6 months then maintained at a mean dose of 68.5 ug daily for another 12 months can cause at least 15% volume reduction in thyroid volume. Carefully designed studies particularly a local study with significant number of patients comparing maintenance levothyroxine vs. discontinuation are needed to provide a clear answer to this important clinical question.

CONCLUSION

We have demonstrated the importance of maintenance with levothyroxine for the shrinkage of thyroid nodules and reduction of thyroid volume. Likewise, further increase in thyroid volume and nodular size can be prevented with this treatment regimen. This benefit can be appreciated if levothyroxine is continued for at least 1 year. Goiter is a lifetime disease and LT4 maintenance therapy to maintain a physiologic level of TSH (0.3 to 1.0 mIU/L) will prevent recurrence. Clearly, prospective and randomized studies to define the issue of long-term maintenance levothyroxine should be done to support this conclusion.

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