THE JOURNAL OF FAMILY PRACTICE

ONLINE EXCLUSIVE

ORIGINAL RESEARCH

Hypothyroidism management: Is an annual check of TSH level always necessary?

Perhaps not. Less frequent measurements may be appropriate for some patients. Our study reveals when you may be able to safely extend the monitoring cycle.

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The authors reported no potential conflicts of interest relevant to this article.

ABSTRACT

Purpose ▶ We conducted this study to identify clinical predictors of normal thyroid-stimulating hormone (TSH) values over a one-year interval in patients treated for hypothyroidism.

Methods ▶ We retrospectively reviewed cases of patients treated for hypothyroidism by the Mayo Clinic Department of Family Medicine in 2006. For patients with a normal TSH value during the initial study period in 2006, we assessed the number who then had therapeutic and nontherapeutic TSH values 10 to 14 months later, and evaluated whether body mass index (BMI), age, sex, or dosage of levothyroxine replacement had predictive value of a normal TSH level.

Results ▶ The percentage of normal repeat TSH values significantly declined with increasing medication dosage (*P*=.01). Of those patients whose maintenance dosage was <75 mcg/d, 90.8% had normal repeat TSH values, compared with just 77.5% of those requiring ≥125 mcg/d, who had significantly lower odds of normal repeat TSH (odds ratio, 0.31; 95% confidence interval, 0.13–0.76; *P*=.01).

Conclusions ▶ Age, sex, and BMI were not predictive of stable TSH values in patients treated for hypothyroidism. The dosage of thyroid hormone replacement was predictive of normal TSH values, with dosages ≥125 mcg/d having significantly decreased odds of a normal repeat TSH on follow-up.

Once the level of thyroid-stimulating hormone (TSH) has been normalized in a patient treated for hypothyroidism, the American Association of Clinical Endocrinologists recommends yearly monitoring.[1] Annual testing has become the default frequency of surveillance for many primary care providers, despite a relative paucity of data to support the recommendation as customary practice.

Factors that can warrant close monitoring of TSH levels. Elderly patients often require lower average doses of levothyroxine replacement of 1 mcg/kg of body weight.[2] Factors that can influence the stability of the TSH level include age, lean body mass changes, pregnancy,[3] and malabsorptive states. Concomitant medications, such as antacids, calcium,[4,5] and selective serotonin reuptake inhibitors,[6] may also affect TSH levels. Various formulations of levothyroxine from different manufacturers may have different bioequivalence; thus a change in brands of medication could affect TSH levels.[7]

Rationale for monitoring TSH levels. Subtherapeutic replacement may not alleviate potential secondary effects of hypothyroidism, including hyperlipidemia, or cardiovascular and neuropsychiatric effects,[8] whereas supratherapeutic replacement is associated with an increased risk of atrial fi-

brillation[9] and decreased bone mass in postmenopausal women.[8,10] Due to the potential hazards of excess thyroxine replacement, as well as the desire to avoid inadequate replacement, it is necessary to monitor the patient's response to replacement. But can the frequency of monitoring vary?

Less frequent monitoring may be acceptable for some. One retrospective study has suggested that an 18-month interval may be more appropriate for patients younger than 60 years taking a levothyroxine dose of 100 to 150 mcg/d.[11] Total health care expenditures for chronic care patients could possibly be reduced by decreasing testing frequency. The objective of this retrospective study was to identify predictors of stable TSH values over one year in patients treated for hypothyroidism, which might allow for a longer monitoring interval.

Patients who require ≥125 mcg/d levothyroxine are less likely than those taking lower dosages to have a normal repeat TSH value in one year.

METHODS

Patient selection

We reviewed the electronic medical records of patients with hypothyroidism treated by the Mayo Clinic Department of Family Medicine from January 1, 2006 through January 1, 2007, and identified a random sample of 780 patients with a documented TSH value in the normal range (0.3-5.0 mIU/L) and no other exclusionary criteria (see below). We reviewed laboratory results to determine if repeat TSH assay(s) were performed during the subsequent 10 to 14 months. We chose this period in an attempt to approximate the one-year interval of monitoring used in standard practice to follow patients with hypothyroidism not requiring dosage changes.

Out of the 780 patients, we identified 452 who had repeat TSH measurements performed 10 to 14 months after documentation of a normal TSH value. We recorded and analyzed demographic data obtained at the time of the first TSH measurement, including age, sex, body mass index (BMI), and thyroxine dose, to determine if there were any identifiable characteristics predicting normal TSH values on repeat screening.

Exclusion criteria. We excluded 328 patients who had normal TSH levels recorded in 2006 but did not undergo a repeat TSH measurement in the subsequent 10 to 14 months or had a repeat TSH measurement done sooner than 10 months that necessitated a change in levothyroxine dosage. We also excluded individuals who were younger than 18 years at the time of the initial 2006 TSH value; who were pregnant during the study period; who had a history of thyroid cancer (due to different recommendations for TSH goals); or who were taking amiodarone or lithium during the study period.

Outcome variables included TSH levels in the therapeutic range vs outside of the therapeutic range. This study was approved under the Mayo Clinic IRB protocol #09-008343.

Statistical analysis

We used a Student's *t*-test to identify any association between age or BMI and a normal repeat TSH value, and a chi-square calculation to test for an association between medication dosage or sex and TSH level at follow-up. We used multiple logistic regression analysis to estimate adjusted odds ratios (ORs) for each independent variable.

RESULTS

Three hundred eighty-six (85.4%) patients were women and 66 (14.6%) were men. Three hundred ten patients were taking levothyroxine at <125 mcg/d, and 142 patients were taking dosages ≥125 mcg/d. At approximately one year, 85.6% of all patients had a normal repeat TSH level.

Results of the 2-way tests are shown in **TABLE 1**. We found no mean differences in age, sex, or BMI between patients with normal repeat TSH levels and those with abnormal levels at follow-up. However, the percentage of normal repeat TSH values was inversely proportional to medication dosage (P=.01). Of patients whose dosage was <75 mcg/d, 90.8% had normal repeat TSH values, compared with 77.5% of patients taking ≥125 mcg/d. Percentages of low, normal, and high TSH values for each dosage range are shown in **TABLE 2**.

These findings were confirmed with multiple logistic regression analysis (**TABLE 3**). Age at index, BMI at index, and sex were not

TABLE 1

Normal TSH levels at one year were more often associated with levothyroxine dosages <125 mcg/d

	TSH normal*	TSH not normal	N	*P* value
Age at index, mean	54.7	54.9	452	.91
BMI at index, mean	28.9	29.0	452	.93
Sex, %				.57
Women	85.2	14.8	386	
Men	87.9	12.1	66	
Total	85.6	14.4	352	
Dosage, mcg/d				.01
0–74.9	90.8	9.2	76	
75–99.9	89.6	10.4	106	
100–124.9	88.3	11.7	128	
≥125	77.5	22.5	142	
Total	85.6	14.4	452	

BMI, body mass index; TSH, thyroid-stimulating hormone.

*Normal range=0.3-5.0 mIU/L.

TABLE 2

Levothyroxine dosages and associated TSH levels* at one year follow-up

Dosage, mcg/d	Low TSH, n (%)	Normal TSH, n (%)	High TSH, n (%)	Total, n
0-74.9	0	69 (90.8%)	7 (9.2%)	76
75-99.9	5 (4.7%)	95 (89.6%)	6 (5.7%)	106
100-124.9	9 (7.0%)	113 (88.3%)	6 (4.7%)	128
≥125	22 (15.5%)	110 (77.5%)	10 (7.0%)	142
Total	36 (8.0%)	387 (85.6%)	29 (6.4%)	452

TSH, thyroid-stimulating hormone.

*Low TSH=<0.3 mIU/L; normal TSH=0.3-5.0 mIU/L; high TSH=>5.0 mIU/L.

significantly associated with normal TSH at follow-up. However, patients with dosages ≥125 mcg/d had significantly lower odds of normal repeat TSH (OR=0.31, 95% confidence interval [CI]=0.13-0.76, *P*=.01).

DISCUSSION

Our retrospective study showed that patients taking <125 mcg/d levothyroxine were likely to have a normal TSH value at one year. Thus we propose that TSH values may be measured less frequently in this population. Given that the fee for testing TSH averages $50, there is potential for savings in costs, as well as in patient and provider time. A prospective, randomized controlled trial of less frequent TSH measurements in asymptomatic patients treated for hypothyroidism with replacement levothyroxine <125 mcg/d would

TABLE 3

Patients with dosages ≥125 mcg/d had significantly lower odds of normal repeat TSH* (N=452)

Variable	Odds ratio	Confidence interval	*P* value
Age at index	0.99	0.98-1.01	.46
BMI at index	1.02	0.98-1.05	.41
Men (vs women)	1.53	0.68-3.48	.31
Dosage, mcg/d			
0–74.9	1		
75–99.9	0.87	0.32-2.37	.79
100–124.9	0.76	0.29-1.97	.58
≥125	0.31	0.13-0.76	.01

BMI, body mass index; TSH, thyroid-stimulating hormone.
*Using multiple logistic regression analysis.

We suggest that TSH levels for patients requiring ≥125 mcg/d levothyroxine be repeated at maximum intervals of 12 months.

yield more definitive conclusions.

Our study also revealed that patients requiring ≥125 mcg/d levothyroxine were less likely than patients requiring lower dosages to have a normal repeat TSH value at one year. The reasons for this are unclear. Although excess body weight may be a reason for patients to be on higher replacement dosages, we did not find BMI to be predictive of continued normal TSH values after one year. Other potential reasons for patients to require higher dosages of thyroid replacement include noncompliance, drug interference, and malabsorption.[12] A change in any of these factors could presumably lead to a change in thyroid replacement needs and a change in TSH upon recheck one year later. Based on this finding, we suggest that TSH levels for patients requiring ≥125 mcg/d levothyroxine be repeated at maximum intervals of 12 months.

Limitations of this study

Study limitations were primarily a consequence of the retrospective design. Selection bias may have occurred by capturing patients with higher compliance. Patients who had repeat testing approximately one year later may reflect a population with more monitoring and better medication adherence. Interestingly, our retrospective review revealed that a large number of patients in our study did not have an annual TSH measurement; out of the 780 patients initially identified with a normal TSH value in 2006, 177 (23%) had repeat TSH values obtained more than 14 months later.

Other limitations of this study include an inability to control for, or detect, any changes in levothyroxine brand between the 2 data points. Because different levothyroxine formulations may differ in bioequivalence, a change in brands between measured values has the potential to affect outcomes.[7] Additionally, the retrospective design could not address whether patients had any concurrent symptoms of over- or undertreated hypothyroidism or had sustained a serious, recent health status change that may have affected their TSH levels. Another limitation was the possible inclusion of women started on levothyroxine replacement for postpartum thyroiditis who may have subsequently recovered full thyroid function but continued on levothyroxine treatment.

Finally, this study design did not control for concurrent medication use other than lithium and amiodarone, thereby potentially overlooking substances such as antacids and calcium that could reduce levothyroxine absorption. However, as a practical matter, use of over-the-counter supplements and substitution in levothyroxine brand are often not reported by patients. JFP

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