Excessive Thyroid Hormone Replacement Therapy

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Background: **Excessive thyroid hormone replacement carries the potential for serious long-term metabolic complications (e.g., accelerated osteoporosis). The increased bioavailability of commercially available products, along with improved laboratory assays for measuring thyrotropin (TSH), has led to an increased chance of actual or detected iatrogenic hyperthyroxinemia. The purpose of this study was to determine the frequency of excessive prescribing and to examine the impact of changes in potency of replacement thyroid hormone formulations and sensitivity of thyroid function tests on its incidence.**

Methods: **A retrospective chart review was done of patients requiring thyroid hormone replacement therapy treated at a university-based, family medicine residency training program. The following information was extracted from each chart: specific thyroid medication (including dose and date of onset of therapy) and thyroid laboratory tests results (including serum thyroxine [T_4] and TSH). This information from two different time periods (1975 to 1981 and 1982 to 1989) was compared using one-way analysis of variance.**

Results: **Serum T_4 levels were not significantly different between the two time periods, 1975 to 1981 and 1982 to 1989 (8.06 ± 2.93 μg/dL versus 9.0 ± 03.69 μg/dL; NS), despite significant changes in TS serum levels (23.6 ± 38.9 mIU/mL versus 7.44 ± 18.7 mIU/mL; $P = 0.009$) and levothyroxine dosage (184 ± 59.6 μg/d versus 145 ± 64.1 μg/d; $P = 0.002$). Significantly more patients had low (supersuppressed) TSH levels between 1982 and 1990 than between 1975 and 1981 (33 percent versus 10 percent; $P = 0.02$.)**

Conclusions: **Excessive thyroid hormone replacement with iatrogenic hyperthyroxinemia is a common occurrence. Clinicians need to be aware of this problem and implement measures (e.g., periodic monitoring of TSH) to minimize the occurrence of overdosing and the potential for long-term complications. (J Am Board Fam Pract 1995; 8:435-9.)**

Thyroid hormone is used as replacement or supplemental therapy in patients who have hypothyroidism from any cause, including functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs. Thyroid hormone can also be used as a pituitary thyrotropin (TSH) suppressant in the treatment of goiters, thyroid nodules, and thyroid cancer. It has long been assumed that replacement therapy, in the absence of symptoms of hyperthyroidism, was without serious adverse effects. From evidence gathered during the past 10 years, however, this claim has been challenged.[1-5] Hypothyroid patients receiving customary, but excessive (defined as supersuppression of TSH) replacement doses of levothyroxine could have subtle but potentially harmful long-term effects on bone mass (loss of both cortical and trabecular bone and osteopenia) similar to the reductions in bone density found in patients with hyperthyroidism.[6-9]

Levothyroxine (as Synthroid, Boots Pharmaceuticals, Inc.) was the fifth most commonly prescribed drug in the United States during 1992.[10] During the past 10 years most manufacturers of levothyroxine have adopted new high-pressure liquid chromatography methods of assaying thyroid hormone content, with subsequent reformulation and increased bioavailability of commercially available products.[11-15] During approximately the same period, laboratory assays for TSH have also improved, becoming more sensitive and more commonly used in clinical practice.[16-19] These concurrent events have led to an increased chance of iatrogenic hyperthyroxinemia (excessive thyroid hormone replacement), as well as its detection. The purpose of this paper is to report the results of an audit of thyroid replacement

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therapy in a university-based family practice clinic and to comment on the frequency of apparent hyperthyroidism (based on laboratory values) resulting from excessive therapy.

Methods

The study was conducted at the Family Medical Center, the model practice site for family medicine residency training at the University of Washington. There are approximately 22,000 patient visits encountered by 18 resident and 14 faculty physicians each year. The charts of all patients who had received thyroid replacement therapy in this setting were reviewed. Two separate computer data bases were searched to select patients. One consisted of records of prescriptions obtained from copies of prescriptions given to patients, which we searched for thyroid hormone prescriptions. The second was a patient visit data base, which we searched for all patients with the diagnosis of hypothyroidism. To be eligible for the study, patients must have had a thyroid-related diagnosis and must have received a prescription for thyroid hormone replacement therapy. Patients with thyroid nodules, thyroid cancer, goiter, or active autoimmune causes of hypothyroidism (Hashimoto thyroiditis) were excluded.

We extracted the following patient-specific information from the medical record: demographics (including age, sex, thyroid-related diagnosis, and date of onset), thyroid medication (including type, dose, and date of onset of therapy), and thyroid laboratory tests results (including serum thyroxine [T_4] and TSH). Data were recorded for each thyroid-related visit during the period from 1975 to 1990. We defined a supersuppressed TSH as a value of <0.4 mIU/mL and elevated levels of T_4 as >10.8 μg/dL, the lower and upper limits of normal, respectively, at the University of Washington Medical Center. The changes in thyroid replacement dose or drug and corresponding laboratory data were examined over time and were aggregated into two different time periods, 1975 to 1981 and 1982 to 1990. This division corresponds to the commercial availability of the more potent thyroid preparations and the increased use of sensitive TSH monitoring. All laboratory values in a single year were averaged for each patient. Patients were monitored from time of first receipt of thyroid replacement therapy until the end of the study. Multiple regression was used to assess the effect of age on thyroid functon, controlling for study periods. Changes in potency of replacement thyroid hormone formulations and sensitivity of thyroid function tests were compared by means of one-way analysis of variance.

Results

In the subsequent chart review we found 98 patients with the diagnosis of hypothyroidism who were receiving thyroid hormone. There were no missing charts. Twenty charts did not meet inclusion criteria primarily because thyroid hormone was being used as suppressant therapy. The remaining 78 charts met all inclusion criteria and contributed 231 patient years of observation. The average number of years of observation for patients initially enrolled between 1975 and 1981 was 4.2, while patients enrolled during 1982 and 1990 were observed for an average of 2.0 years.

The average age of all patients was 54.1 years (range, 20 to 91 years). Patients observed during the period from 1975 to 1981 were significantly older (average, 65 years) than patients observed during the period from 1982 to 1990 (average, 52.6 years; $P=0.001$). The average weight was 156.5 pounds (range, 97 to 310 pounds). Seventy-six percent of the patients were women. Hypothyroidism requiring replacement therapy was the most common diagnosis (79.2 percent of patients). The remaining 20.8 percent of patients were receiving replacement therapy following surgical removal of the thyroid gland or radioactive ablation for Graves disease. Table 1 lists the types and frequency of thyroid hormone replacement prescribed. Levothyroxine was the most frequently prescribed thyroid hormone preparation (77.6 percent of patients).

Table 1. Thyroid Replacement Therapies Utilized.

Preparation*	Patient Observations No. (%)
Thyroid extract	32 (14.0)
Levothyroxine	177 (77.6)
Liothyronine-levothyroxine	11 (4.8)
Thyroglobulin	7 (3.1)
Liothyronine	1 (0.4)

*Type of thyroid replacement prescribed missing for 3 patients.

The mean T_4 and TSH levels and levothyroxine dosages for each period are shown in Table 2. There was a substantial difference between the two groups in the number of patients with recorded T_4 and TSH levels. For patients studied in the period from 1975 to 1981, only 23.1 percent had a recorded T_4 level and 38.5 percent had a recorded TSH level. During the period from 1982 to 1990, the number of recorded T_4 and TSH levels were more common (T_4, 68.9 percent; TSH, 83.7 percent). In 231 patient-years of observation, 206 (89.2 percent) had a dose of levothyroxine recorded in charts studied. Twenty-six were recorded in the period from 1975 to 1981 and 180 in the period from 1982 to 1990. There was also a substantial difference between the two groups in the number of patients with recorded T_4 and TSH levels, perhaps reflecting the changes in practice patterns over time. Only 56 percent of patients had at least one serum T_4 level per year recorded. Nearly one-half (48 percent) of our patients on replacement therapy had serum TSH levels <0.4 mIU/mL for 1 year (10 percent for 2 years).

When the two study periods (1975 to 1981 and 1982 to 1990) were compared, mean serum T_4 levels were unchanged (8.06 ± 2.92 μg/dL versus 9.00 ± 3.69 μg/dL; NS) despite significant changes in mean TSH (25.2 ± 38.9 mIU/mL versus 7.44 ± 18.7 mIU/mL; $P=0.009$) and levothyroxine dosage per day (184 ± 59.6 μg/d versus 145 ± 64.1 μg/d; $P=0.002$). More patients had low (supersuppressed) TSH levels between 1982 and 1990 than between 1975 and 1981 (33 percent versus 10 percent; chi square analysis, $P=0.02$, n=160 person-years of observation with recorded data [Figure 1]). The results of multiple regression indicated no relation of age to either TSH or T_4 after controlling for the study period.

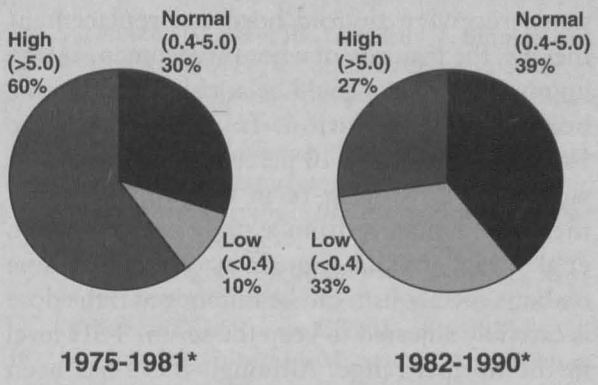

Figure 1. Averaged patient thyrotropin (TSH) levels based on mean yearly TSH levels for each subject (in mIU/mL). *Statistically significant at $P < 0.02$.

Discussion

Abnormal bone and mineral metabolism is well documented in states of thyroid hormone excess.[20,21] Thyroid hormone directly stimulates osteoclastic bone resorption. This ultimately leads to a negative calcium balance. In an earlier study the bone densities of 31 premenopausal women who had been taking thyroid hormone for at least 5 years were compared with those of 31 aged-matched women without thyroid disease.[22] The thyroid-hormone-treated group was found to have significantly lower bone density at the femoral neck and trochanter. The changes were most striking in women older than 35 years. These findings have been corroborated in other studies.[4-6,8,9] Jennings, et al.[7] proposed that iatrogenic hyperthyroxinemia (excessive thyroid hormone replacement) could result in diminished bone density, which could potentially occur at doses that do not cause clinical hyperthyroidism. Excessive thyroid hormone replacement is defined as a TSH level that has been supersuppressed (<0.4 mIU/mL). Theoretically, the increased potency of thyroid hormone preparations available since 1982 could result in a greater number of patients at risk for excessive therapy. Given the large number of pa-

Table 2. Average Thyroxine Function Tests and Levothyroxine Dosage by Year.*

Thyroid Function Tests	1975–81	1982–90	Total Observations	*P* Value†
$T_4 \pm$SD (μg/dL)	8.1 ± 2.9 (n=6)	9.0 ± 3.7 (n=124)	130	0.54
TSH ±SD (mIU/mL)	25.2 ± 38.9 (n=10)	7.4 ± 18.7 (n=150)	160	0.09
Levothyroxine equivalent (μg/dL)	176.9 ± 63.2 (n=26)	135.7 ± 60.7 (n=180)	206	0.004

*Based on person-years of observation.
†Student t-test.

tients receiving thyroid hormone replacement therapy, the majority of whom are women, a large number of patients could be at risk for iatrogenic bone demineralization. In a survey of the Framingham cohort, 10 percent of older women were receiving long-term thyroid hormone therapy.[23] Evidence from a study by Greenspan, et al.[24] suggests that the effects of levothyroxine on bone metabolism can be minimized if the dose is carefully adjusted to keep the serum TSH level in the normal range. Although there has been controversy about the chemical equivalence and bioequivalence of levothyroxine tablets in the past, there was insufficient use of alternative thyroid formulations in this study to allow such a comparison. Many reports have shown lack of bioequivalence; other investigators have reported equivalence.[12-14, 25-29] It appears that most manufacturers of levothyroxine have taken steps to overcome this problem.[10] The more sensitive TSH assay should allow for easier detection of excessive therapy. In the 1975–1981-year group, only 6 (23.1 percent) of 26 patients had a recorded T_4 level and 10 (38.5 percent) had a recorded TSH level compared with 124 (68.9 percent) of 180 patients with a T_4 recorded and 150 (83.3 percent) with a TSH recorded during the 1982–1990 period.

Data were not available and the period of observation was too short in some cases to confirm earlier observations on the long-term effects of hyperthyroxinemia (e.g., accelerated osteoporosis). We believe to do so would require a cohort or case-control report. We lost some patients to follow-up when they changed to other providers and moved out of the area. Of course, we cannot account for patients overlooked if our data base searching techniques failed to pick out all eligible patient records.

The purpose of this report was to review retrospectively the records of all patients in a teaching family practice clinic for evidence of excessive thyroid replacement therapy. From the results of our investigation, we conclude the following: (1) More potent formulations of levothyroxine are being used in clinical practice, as was manifested by a decrease in TSH levels and increase in T_4 levels despite a decreased dose of replacement therapy. (2) A substantial number of patients fit the criteria for receiving excessive therapy as indicated by supersuppressed levels of TSH. Nearly one-half (48 percent) of our patients receiving replacement therapy had serum TSH levels < 0.4 mIU/mL for 1 year (10 percent for 2 years). (3) Although we do not report information specifically, there was a wide variation in how physicians utilized the laboratory in monitoring thyroid replacement therapy. Recent reports have suggested guidelines that might allow for a more uniform approach to patients on long-term thyroid hormone replacement.[9,15,19] Based on these findings and our review of this literature, we recommend the following:

1. Initiate therapy at a lower dosage range. In general, the recommended starting dose for replacement therapy is 1.8 μg/kg. Because T_4 clearance declines throughout life, older adults will need approximately 60 percent of this dose.[23]
2. Order TSH assays for patients receiving replacement therapy approximately once each year after the patient has become stabilized.[16-19] From 6 to 12 weeks are required after starting a patient on levothyroxine for thyrotropin levels to stabilize at a new steady-state level; therefore, after initiating therapy or after a dose adjustment, the clinician should wait for an appropriate period before arranging follow-up testing. There are no published data to serve as a guideline for monitoring thyroid function in stable patients on replacement therapy.
3. Do not routinely order serum T_4 measurements, because they are unnecessary. The sensitive TSH assay and the new formulations of thyroid hormone facilitate better titration for a given patient.

Conclusion

When prescribing thyroid hormone for patients requiring replacement therapy, clinicians should consider the potential for inadvertent excessive treatment. Current levothyroxine formulations are more potent. The sensitive TSH assay can be used to titrate a proper dose accurately for a given patient. Long-term monitoring should be incorporated into the health care maintenance of patients on thyroid hormone replacement therapy.

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