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Surgical Treatment of Hyperthyroidism Can Be Performed Safely Before a Euthyroid State is Achieved

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WHILE ONLY 1.2% OF the U.S. population suffers from hyperthyroidism, this condition is costly to both the patient and the health care system.^{1,2} The underlying pathology is most commonly secondary to Graves' disease,

less common causes of hyperthyroidism include autoimmune diseases, drug-induced, or postpartum effects.³ Treatment for hyperthyroidism includes both medical and definitive therapies such as radioactive iodine and surgical thyroidectomy,⁴ each conferring their own risks and benefits. The goal of these

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and lower risk of... (11%) (0.5% vs. 11%; $p < 0.001$), respectively. Uncontrolled patients were more likely to be diagnosed with Grave's disease (85.1% vs. 67.9%, $p < 0.001$) and to undergo surgery due to medication intolerance (12.1% vs. 6%) or history of thyroid storm (6.4% vs. 1.5%) ($p = 0.008$).

- While only 1.2% of the U.S. population suffers from hyperthyroidism, this condition is costly to both the patient and the health care system. The underlying pathology is most commonly secondary to Graves' disease, followed by toxic multinodular and single adenomas.
- less common causes of hyperthyroidism include autoimmune diseases, drug-induced, or postpartum effects

- Treatment for hyperthyroidism includes both medical and definitive therapies such as radioactive iodine and surgical thyroidectomy
- methimazole and propylthiouracil is associated with known side effects of hepatotoxicity, agranulocytosis and congenital defects.
- Radioactive iodine is contraindicated in patients with **thyroid eye disease and in patients who are pregnant, desire a pregnancy in the near future, or are unable to maintain 6 feet of distance from pregnant women or infants in their household.**
- In addition to the aforementioned side-effects, medical and radioactive therapies often require weeks to months (if ever) to achieve biochemical and symptomatic resolution, and may even require repeated treatments.

- ✧ If surgical intervention is deemed most appropriate, the 2016 American Thyroid Association Guidelines state that hyperthyroid patients should be rendered euthyroid before surgery to prevent thyroid storm (strong recommendation, low- quality evidence)
- ✧ These recommendations are based on low quality and limited evidence.
- ✧ It is hypothesized that storm is likely precipitated by gland **manipulation**, leading to excess hormone release into the patient's bloodstream. It has also been suggested that **anesthesia** itself can precipitate thyroid storm, though data on this are limited.

- ❧ While achieving the euthyroid state is **ideal**, patient-related factors, such as **allergies to medications, drug side effects, refractory disease, compliance with therapy, and the urgency in which definitive therapy is needed, are critical** in determining whether or not hyperthyroidism can be controlled preoperatively.
- ❧ Due to the medically underserved nature of our patient population and our position as the only highvolume, quaternary academic referral center in the state, many of our patients are unable to achieve euthyroid status.

- ❧ Questions remain regarding the safety and efficacy of surgery in the actively hyperthyroid state.
- ❧ With this in mind, we compared peri-and post-operative outcomes for patients with both controlled and uncontrolled hyperthyroidism at the time of thyroidectomy.
- ❧ Our hypothesis was that surgery could be performed before achieving euthyroid state in hyperthyroid patients without compromising postoperative outcomes.

Methods

- we performed a retrospective cohort study of 275 hyperthyroidism patients undergoing thyroidectomy from December 2015 to November 2022.
- Inclusion criteria:
 - undergoing thyroidectomy at our institution,
 - being >18 years of age
 - having a diagnosis of hyperthyroidism documented in the medical record.
- In addition to a documented diagnosis, the included patients had either a suppressed **preoperative** TSH or T3/T4 elevation

- Four faculty surgeons participated in this study, all of whom are high-volume endocrine surgeons.
- Patients were **defined as uncontrolled** if T3 or T4 was elevated immediately before surgery (normal=2.8–4.4pg/mL, 0.58–1.64ng/dL, respectively).
- Electronic medical records were examined to classify patient demographics, disease etiology, patient-reported reason for surgery, preoperative medication(s), operation length, intraoperative blood loss, and postoperative outcomes.

Temporary hypocalcemia was defined as calcium <8.4 mg/dL (range 8.4–10.2), normalizing by 6 months postoperatively, and liberated from calcium supplementation. **Permanent hypocalcemia** was defined as continued need for calcium supplementation by most recent postoperative visit, ≥ 6 months post operatively.

Similarly **temporary hoarseness** was defined as patient-reported voice changes, with resolution achieved by 6 months postoperatively. **Permanent hoarseness** was defined as patient-reported voice changes without resolution at the most recent followup, >6 months postoperatively

- ❧ Hematoma was classified as those patients requiring operative evacuation.
- ❧ We defined **thyroid storm** according to the Japan Thyroid Association Definition and Diagnostic Criteria, which includes **(1) the presence of thyrotoxicosis** with elevated levels of fT3 or T4 in addition to **(2) evidence of end-organ failure**, resulting from break down of physiologic compensation mechanisms.
- ❧ Some **stigmata of thyroid storm** can include derangements in the central nervous system, fever, tachycardia or arrhythmia, congestive heart failure, or gastrointestinal and hepa-tobiliary manifestations.

- ❧ We made comparisons between groups using Wilcoxon Rank Sum test and Chi-square tests, as appropriate.
- ❧ R (version 4.2.1, 2022) software was used for data analysis. Associations were considered significant at $p < 0.05$.

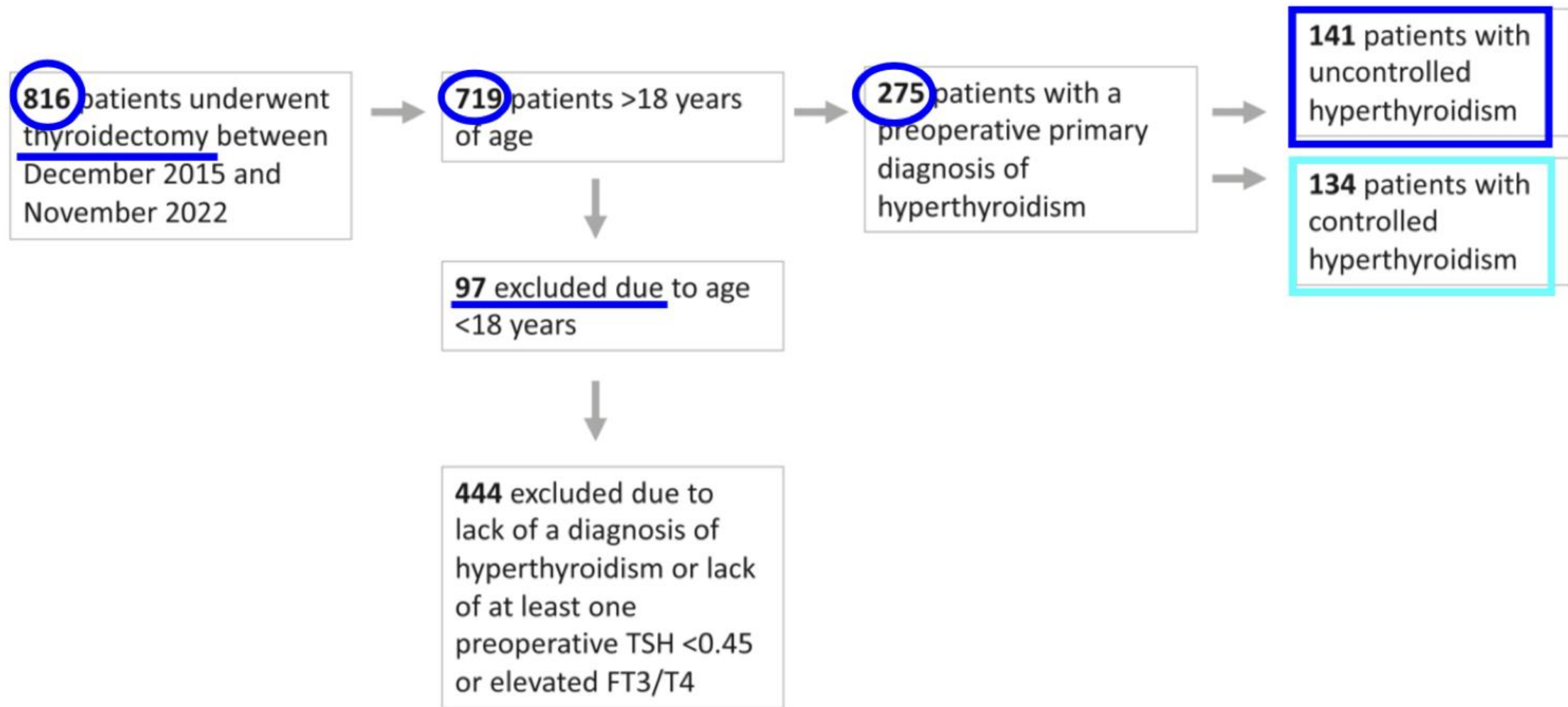


FIG. 1. Participant flow diagram.

Results

- Of the 275 patients, 84.3% were women and 51.3% were uncontrolled at time of surgery.
- Controlled patients had higher median TSH (0.4 [0.0, 2.4] mIU/L vs. 0.0 [0.0, 0.0] mIU/L, $p < 0.001$) and lower fT4 (0.9 [0.7, 1.1] ng/dL vs. 3.1 [1.9, 4.4] ng/dL, $p < 0.001$), respectively.
- Uncontrolled patients were more likely to be diagnosed with Grave's disease (85.1% vs. 67.9%, $p < 0.001$) and to undergo surgery due to medication intolerance (12.1% vs. 6.0%) or history of thyroid storm (6.4% vs. 1.5%, $p = 0.008$).

- Uncontrolled patients were also more likely to take a **larger number** of preoperative medications [2.3 (−1.0) vs. 1.4 (−0.8), $p < 0.001$].
- Preoperatively, uncontrolled patients were more commonly prescribed anti-thyroid medication (89.4% vs. 72.4%, $p = 0.009$), beta-blockers (61.0% vs. 45.5%, $p < 0.001$), steroids (31.2% vs. 7.5%, $p < 0.001$), and Lugol's solution (7.8% vs. 2.2%, $p = 0.036$) (Table 1).

- ❧ **Eleven** patients already admitted to the hospital and found to be in thyroid **storm before operation** were included in postoperative outcomes assessment, **nine** of whom were **un-controlled** at the time of surgery.
- ❧ Of those patients **not** already in thyroid storm, **no patient in either the controlled or un-controlled groups progressed to storm during the perioperative period.**
- ❧ Controlled patients had **shorter operative times** (19.8% vs. 7.3% <1 hour, $p = 0.014$) and decreased **median estimated blood loss** (15.0 [5.0, 30.0] mL vs. 20.0 [10.0, 50.0] mL, $p = 0.002$).

- Both groups experienced similar, low rates of postoperative complications.
- Temporary hypocalcemia was more prevalent in the uncontrolled group (13.4% vs. 4.7%, $p = 0.013$). Permanent hypocalcemia was experienced by 0 patients in the controlled group, and 4 patients in the un-controlled group ($p = 0.137$).
- Temporary hoarseness was noted in 6.6% of the control group and 5.0% of the uncontrolled group ($p = 0.531$). Permanent hoarseness was noted in 1 patient from each group ($p = 0.967$) (Table 2).

TABLE 1. DEMOGRAPHICS

	<i>Controlled (N=134)</i>	<i>Uncontrolled (N=141)</i>	p
Age	50.5 (37.0, 61.0)	39.0 (31.0, 55.0)	<0.001
Median (Q1, Q3)			
Sex (female)	113.0 (84.3%)	108.0 (76.6%)	0.107
Pathology			
Toxic nodule(s)	43.0 (32.1%)	21.0 (14.9%)	<0.001
Graves	91.0 (67.9%)	120.0 (85.1%)	
Reason for surgery			0.008
Allergy to medications	1.0 (0.7%)	6.0 (4.3%)	
Intolerance to medications	8.0 (6.0%)	17.0 (12.1%)	
Refractory symptoms	123.0 (91.8%)	109.0 (77.3%)	
Thyroid storm	2.0 (1.5%)	9.0 (6.4%)	
Medications			
Mean no. (SD)	1.4 (0.8)	2.3 (1.0)	<0.001
Anti-thyroid drugs	97.0 (72.4%)	126.0 (89.4%)	<0.001
Beta blockade	61.0 (45.5%)	86.0 (61.0%)	<0.001
Steroids	10.0 (7.5%)	44.0 (31.2%)	<0.001
Lugol's iodine	3.0 (2.2%)	11.0 (7.8%)	0.036
Preoperative TSH (mIU/L)			
Median (Q1, Q3)	0.4 (0.0, 2.4)	0.0 (0.0, 0.0)	<0.001
Preoperative T4 (ng/dL)			
Median (Q1, Q3)	0.9 (0.7, 1.1)	3.1 (1.9, 4.4)	<0.001
Preoperative T3 (ng/dL)			
Median (Q1, Q3)	3.6 (3.1, 3.9)	6.2 (4.8, 12.3)	<0.001
Preoperative calcium (mg/dL)			
Median (Q1, Q3)	9.5 (9.2, 9.8)	9.6 (9.1, 9.8)	0.467
Preoperative T4 quartiles (ng/dL)			
Quartile 1 [0.125, 0.855]	64.0 (47.8%)	5.0 (3.5%)	<0.001
Quartile 2 [0.855, 1.27]	57.0 (42.5%)	12.0 (8.5%)	
Quartile 3 [1.27, 3.12]	13.0 (9.7%)	55.0 (39.0%)	
Quartile 4 [3.12, 25]	0.0 (0.0%)	69.0 (48.9%)	

SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin.

TABLE 2. OPERATIVE CHARACTERISTICS AND PATIENT-RELATED COMPLICATIONS

	<i>Controlled</i> (N=134)	<i>Uncontrolled</i> (N=141)	p
Operative time (hours)			
<1	25.0 (19.8%)	9.0 (7.3%)	0.014
1-2	57.0 (45.2%)	54.0 (43.9%)	
2-3	37.0 (29.4%)	47.0 (38.2%)	
>3	7.0 (5.6%)	13.0 (10.6%)	
Estimated blood loss (mL)			
Median (Q1, Q3)	15.0 (5.0, 30.0)	20.0 (10.0, 50.0)	0.002
Complications			
Hypocalcemia			
Temporary	6.0 (4.7%)	18.0 (13.4%)	0.013
Permanent	0.0 (0%)	4.0 (3.0%)	0.137
Hematoma (evacuation)	1.0 (0.7%)	5.0 (3.5%)	0.112
Hoarseness			
Temporary	10.0 (6.6%)	8.0 (5.0%)	0.549
Permanent	1.0 (0.8%)	1.0 (0.7%)	0.967

Discussion

- ❧ Thyroid storm is a life-threatening complication of hyperthyroidism. it is postulated that a physiologic insult precipitates the transformation of simple thyrotoxicosis to an overwhelming release of thyroid hormone.
- ❧ Historically, the trauma from surgical thyroidectomy was thought to represent such a potential insult. As a result of these widely adopted hypotheses, the 2016 American Thyroid Association guidelines state “If surgery is chosen as treatment for Graves’ Disease, patients should be rendered euthyroid prior to the procedure.”
- ❧ However, evidence to support this recommendation is lacking in the literature.

- Early operation on hyperthyroid patients has been shown to improve biochemical recovery and has not been associated with increased complications in previous studies.
- We hypothesized that **delaying operation** in this patient population to achieve euthyroid state would result in increased cost and distress in patients due to continual symptomatology, chronic medical therapy, and even inpatient hospitalizations.
- Importantly, a euthyroid state may not be achievable in many patients for a variety of reasons, including (but not limited to) medication **intolerance** or **non-adherence**.
- In addition, we hypothesized that medically underserved populations would have more difficulty achieving euthyroid state due to issues of access and affordability of treatment, though data in this regard are limited. This is anecdotally the case in our patient population, as >15% of Alabaman's live below the poverty line.

Patients in lower socioeconomic strata have been shown to have greater incidence of clinical manifestations best treated with surgery, such as ophthalmopathy and higher severity of disease, thus demonstrating that this is a group that could benefit especially from timely referral to surgical care.

- ❧ In 2021, our group performed a small study demonstrating the safety of operating on Graves' disease patients who were hyperthyroid at the time of operation. No patients in our study developed overt thyroid storm as a result of surgery.
- ❧ This conclusion was also borne out in a similar retrospective cohort study by Al Jassim et al. in 2018. Their findings similarly show that no biochemically hyperthyroid patients converted to thyroid storm in the perioperative period.

❧ A 2021 systematic review examining surgery for primary hyperthyroidism examined 26 retrospective and prospective cohort studies, Twelve of those studies included data on preoperatively controlled versus uncontrolled hyperthyroid patients. **Thyroid storm did not occur in either group in any of the literature reviewed.**

- **We** have, with this **retrospective** review, contributed the **largest** study to date demonstrating the safety of operating in the hyperthyroid state.
- In our 275-patient cohort, **more than half were actively hyperthyroid at the time of operation**, with **no significant difference in low rates of permanent postoperative complications or incidence of thyroid storm.**

- ⤴ Though **perioperative** complications such as **blood loss and operative time were increased in uncontrolled hyperthyroid** patients, one could argue this as an expected, has no effect on clinically important patient outcome.
- ⤴ hyperactive glands are often goitrous, woody/inflamed, and demonstrate increased vascularity, making the administration of a saturated iodine solution (Lugol's) to decrease vascular supply an attractive choice to some clinicians.
- ⤴ administration of **Lugol's** solution is **not routine practice at our institution**. In addition, some data demonstrate that it does not change surgical outcome

- The uncontrolled hyperthyroid patients exhibited a significant but temporary increase in rates of postoperative hypocalcemia (13.4% vs. 4.7%).
- We postulate that the **degree of postoperative hungry bone syndrome is more severe in the uncontrolled group and accounts for much of the observed hypocalcemia rather than hypoparathyroidism alone.**

limitation

- it is our practice to routinely administer steroids on anesthetic induction to reduce conversion of circulating fT4 to T3.
- The results of this study may not be generalizable in settings without access to skilled and experienced anesthesiologists, leading to selection bias in our reporting.
- Our data are also limited to patients who were eligible for surgical intervention, one potential source of selection bias in our study.
- Lastly, in this study, we used the Japanese Thyroid Association (JTA) criteria¹¹ to define thyroid storm rather than the Burch Wartofsky Point Scale (BWPS). It is known that the JTA is **less sensitive** than the BWPS in diagnosing thyroid storm, and potential underdiagnosis of this condition in our dataset is a limitation of our study.

Conclusions

- ↳ Thyroidectomy can be performed safely and without precipitating thyroid storm in actively hyperthyroid patients. Therefore, surgical evaluation of hyperthyroid patients should not be limited to only those in the euthyroid state.