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Clinical Thyroidology® for the Public

VOLUME 12 | ISSUE 7 | JULY 2019

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EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room. Also check out our friends in the **Alliance for Thyroid Patient Education**. The **Alliance** member groups consist of: the *American Thyroid Association, Bite Me Cancer, the Graves' Disease and Thyroid Foundation, the Light of Life Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International*.

The American Thyroid Association (ATA) extends its appreciation to all of the patients and their families that are part of the ATA community — our **Friends of the ATA**. It is for you that the ATA is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer.

July is Graves' Disease Awareness Month.

We have 2 special articles in this issue. The first is a memorial of the life of Dr. Lewis E. Braverman, a giant in the field of Thyroidology who recently passed away. The second is a guest blog from Dr. Elizabeth Pearce on behalf of the Iodine Global Network.

In this issue, the studies ask the following questions:

- Do thyroid antibodies predict relapse in patients with Graves' disease?
- Are side effects of antithyroid drugs more common in patients with amiodarone-induced thyrotoxicosis?
- Should thyroidectomy be considered in some patients with Hashimoto's thyroiditis?
- Are NIFTP tumors really benign?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

— Alan P. Farwell, MD, FACE

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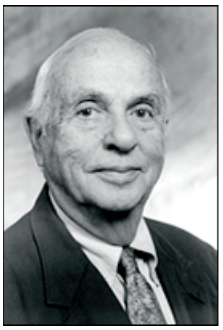
IN MEMORIAM

Lewis E. Braverman, MD, MACE, MACP



On June 10, 2019, Dr. Lewis E. Braverman passed away at the age of 90, leaving a tremendous legacy in the thyroid field. Dr. Braverman was born in Quincy, MA and graduated from Milton Academy and Harvard College. He received his MD from Johns Hopkins University School of Medicine, followed by a Residency at Boston City Hospital and an Endocrinology Fellowship under the direction Sidney H. Ingbar, MD in the Thorndike Memorial Laboratory, the first clinical research laboratory in a city hospital in the country. He was Chief of Endocrinology at St. Elizabeth's Hospital in Boston, founding Director of Endocrinology and Chief of Nuclear Medicine at the University of Massachusetts Medical Center in Worcester and Chief of Endocrinology, Diabetes and Nutrition at Boston Medical Center/Boston University. He actively saw patients in the Endocrine clinic at Boston Medical Center until January 2018 when he retired from clinical practice at the age of 88.

Dr. Braverman was a prolific thyroid researcher with >600 publications in many leading clinical and research medical journals. He served on many NIH study sections and advisory committees and was the Principal Investigator on several long-standing clinical and research studies. His seminal demonstration that thyroxine was converted to triiodothyronine in humans was published in the *Journal of Clinical Investigation* in 1970. In 1982, he identified a new genetic disorder, familial dysalbuminemic hyperthyroxinemia, that could be confused with thyrotoxicosis. In 1987, he discovered the etiology of an outbreak of thyrotoxicosis in the midwest was due to the inclusion of cow thyroid gland in several meat processing plants in the manufacturing of hamburger. This discovery led to a change in meat processing. He was an international expert in iodine metabolism, most recently publishing the results of iodine nutrition studies in Haiti in 2018 and in Armenia (currently in press). He was longtime co-editor of the leading thyroid textbook, ***The Thyroid: A Fundamental and Clinical Text***, and was actively working on the 11th edition at the time of his death.

Dr. Braverman was an active and dedicated member of the major endocrine societies over his long career. His "home" society was the American Thyroid Association where he served as Secretary and President. He was the recipient of all of the major awards of the American Thyroid Association, the Endocrine Society and the American Association of Clinical Endocrinologists. He served as Editor-in-Chief of the *Journal of Clinical Endocrinology and Metabolism and Endocrine Practice*. He was named Masters of the American College of Endocrinology and the American College of Physicians.

While Dr. Braverman led an illustrious academic career and owns a place with the giants in the field of Thyroidology, his most important legacy is the more than 70 fellows he has directly mentored as well as the hundreds others who have passed through his laboratory and his clinic over the years. He dedicated his life to his passion for training and supporting fellows, residents, students and junior faculty. He encouraged them along their lifelong journey of gaining knowledge and expertise while fostering the joy and satisfaction that led all of us to pursue medicine and science as a career, not only in the field of Thyroidology, but in all aspects of medicine. The leadership and guidance he provided to his fellows over his career inspired a lifelong drive for excellence in all our endeavors. In honor of his lifetime of mentorship, the American Thyroid Association established the Lewis E. Braverman Distinguished Award Lectureship in 2011. This award "recognizes an individual who has demonstrated excellence and passion for mentoring fellows, students and junior faculty; has a long history of productive thyroid research; and is devoted to the ATA". It was his passion for mentoring fellows, students and junior faculty that most defined Dr. Braverman and truly places him among the giants.

Despite his prodigious research career, Dr. Braverman always maintained an active clinical practice. His clinic notes were always handwritten and he never gave in to the electronic demands of current day clinical documentation. However, when disaster struck a few years ago and the computer systems went down for ~1 week, he was

IN MEMORIAM: LEWIS E. BRAVERMAN, MD, MACE, MACP, continued

the only individual who did not miss a beat in seeing his patients, since all of his notes were in his shadow charts! He also called all of his patients personally with their test results, usually starting ~6AM on Sunday mornings!

He was beloved by his patients, who were devoted and loyal to him, with many following him as he moved to various institutions during his career. After the news of his retirement from clinical practice became known, our office frequently received "fan mail" for Dr. Braverman. The notes and letters inside were not simply expressions of well wishes and thanks from his patients, but were tributes to his skill, his kindness and sincerity, to the way he made them feel cared for and the lovely way he had of inserting himself into the lives of the people around him. They expressed appreciation that he knew the names of their children and grandchildren, that he inquired about other aspects of their lives besides their health and, of course, wrote of how very much they would miss him.

Not only did his patients grieve the loss of having him in their lives, but his staff did as well. Regardless of how busy the clinic was, Dr. Braverman always took the time to thank those who supported him at work. He asked about their families, told them how much he appreciated their help and always advocated for them to managers and leaders. In return, they adored him and always made an effort to make his clinic sessions go as smoothly as possible. These relationships, not just with colleagues and trainees, but also with his patients and staff are what made him the truly special and unique man we all miss.

I would like to end on a more personal note. Over the years, my in-laws would frequently cite "Dr. Braverman" when dispensing medical advice. The Dr. Braverman in question was Dr. Harry Braverman, Lew's father who was a general practitioner in Quincy, MA. My in-laws lived in Quincy for a short time where Harry Braverman delivered my wife's older brother and sister. While my in-laws had Dr. Harry Braverman as their doctor for only 6 years, he became their gold standard for a physician throughout their lives. With this legacy as a father, it is no wonder that Dr. Lewis Braverman became the "gold standard" of a researcher, clinician, director and mentor for all of us.

He will be deeply missed as a confidante, advisor, colleague, mentor, physician and, most of all, as my very dear friend.

— Alan P. Farwell, MD, FACE

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Guest Blog from the Iodine Global Network

Timing matters for healthy iodine nutrition in the development of verbal IQ in babies during pregnancy. Recent studies suggest that, in the first trimester and at least three months prior to conception, pregnant women should consume 150 µg of iodine a day.

Levie D et al. Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data. J Clin Endocrinol Metab. Epub 2019 Mar 28. PMID: 30920622

In a recent study of 6,180 mother-and-child pairs from the Netherlands, Spain, and the UK, pregnant women with healthy levels of iodine intake (>150 mcg a day) during the first trimester gave birth to newborns with higher verbal IQ than women with a lower iodine intake. This study suggests that healthy levels of iodine, a critical nutrient for production of thyroid hormone, were associated with higher child verbal IQs.

This has serious implications for countries like the U.S., where mild iodine deficiency may be widespread in pregnancy despite evidence that the population as a whole is getting adequate iodine nutrition.

So, how do we make sure women get adequate iodine nutrition and ensure the health and vitality of their newborns?

During pregnancy, iodine is essential for the production of thyroid hormones in both the mother and the baby. Thyroid hormone plays a critical role in growth and development of the baby during pregnancy. Thyroid hormone from the mother crosses the placenta to the baby early in the first trimester, before the baby's thyroid is functioning. Through its contribution to thyroid hormone production, iodine supports growing baby's bones, tissues, and brain cells.

While it's already been established that severe maternal iodine deficiency can lead to lower IQ in the baby, this study revealed that even mild to moderate nutritional deficiency in iodine can impact brain development during pregnancy. And, significantly, iodine intake is critical through the first 14 weeks of pregnancy. Thus, for the developing baby, timing matters. Not only is it critically important in the first trimester, but in the family planning stages – ideally women need adequate iodine intake at least three months before becoming pregnant.

Compounding the challenges is that the U.S. is missing an opportunity to protect future generations through the foods we already eat. Unlike nearly two-thirds of the countries in the world, the U.S. does not mandate fortification of salt with iodine. Globally, many pregnant women now consume healthy amounts of iodine through this simple, effective and population scalable intervention: universal salt iodization.

This is the focus of the Iodine Global Network's advocacy, and has led to a drastic decline globally in iodine deficiency disorder, which can have debilitating and life-long affects for newborns, including brain impairment and stunted growth.

For pregnant and breast-feeding women in the U.S., the American Thyroid Association and the American Academy of Pediatrics recommends supplementing a healthy diet with 150 µg of iodine a day to support healthy growth. This should protect pregnant women and their children from the effects of iodine deficiency, but it is not the ideal long-term solution for the U.S. population, since not all pregnancies are planned and not all pregnant women are aware of this advice.

At the Iodine Global Network we'll continue to advocate for the U.S. to mandate iodized salt, even as we urge consumers to choose iodized salt, and dispel some of the myths around non-iodized salt. In the meantime I'll be advising my fellow clinicians to recommend that U.S. patients who are planning pregnancy, pregnant, or lactating supplement with iodine for healthier newborns.

— Elizabeth Pearce, MD
President, American Thyroid Association, Regional Coordinator, North American for the Iodine Global Network

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HYPERTHYROIDISM

Antithyroid drug–induced agranulocytosis is about 10-fold more common in amiodarone-induced thyrotoxicosis than in thyrotoxicosis due to other causes

BACKGROUND

The antithyroid drugs methimazole (MMI) and propylthiouracil (PTU) are used to treat hyperthyroidism. While these drugs are usually well tolerated, they do have side effects. The most severe side effect is agranulocytosis, which is a severe decrease in white blood cells that fight infection causing an increased risk of developing a serious infection. Agranulocytosis is very rare, occurring in 0.2-0.5% of treated patients.

Amiodarone is a medication used to treat irregular heart rhythms. It contains a very high amount of iodine that can cause thyroid problems. It can cause thyrotoxicosis either due to too much thyroid hormone production or leakage from the gland. This is treated with antithyroid drugs (ATDs), steroids, or both. The researchers performed this study to compare the ATD-associated agranulocytosis risk in amiodarone-induced thyrotoxicosis (AIT) patients with those who had thyrotoxicosis from other causes (non-AIT).

THE FULL ARTICLE TITLE

Gershinsky M et al 2019 Increased risk of antithyroid drug agranulocytosis associated with amiodarone-induced thyrotoxicosis: a population-based cohort study. Thyroid 29:193–201. PMID: 30648930.

SUMMARY OF THE STUDY

The study was done using the largest health services provider database in Israel (Clalit Health Services). Patients 18 years and older who had a diagnosis of thyrotoxicosis, hyperthyroidism, thyroid nodule, thyroid goiter, or benign nodule of the thyroid who received a prescription for ATDs between January 1, 2002 and December 31, 2015 were studied. Those with cancer, transplantation, lupus, bone marrow disease, or had been treated with medications that can affect the immune system were excluded.

There were 14,781 patients who had received treatment with ATDs for thyrotoxicosis. In 593 patients (4%) the thyrotoxicosis was attributed to amiodarone treatment. These patients were older and more obese than those with non-AIT, there were more males and more smokers. Other medical problems, including hypertension, diabetes, and renal failure were more common. These patients were also taking other drugs for heart problems.

In the first year of ATD treatment, 8 patients (1.3%) with AIT and 20 patients (0.14%) with non-AIT developed ATD-induced agranulocytosis. A total of 1 patient with AIT and 3 with non-AIT died. The starting dose of the ATDs were higher in patients with AIT and with patients who developed ATD-induced agranulocytosis.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Patients with amiodarone-induced thyrotoxicosis were at higher risk to develop ATD-induced agranulocytosis compared to patients with non-AIT. AIT patients with ATD-induced agranulocytosis were older, had more health problems, and were taking more heart medications. This is the first study showing that the risk for a potentially life-threatening side effect of ATDs is higher in AIT patients. More studies in several different populations are needed to confirm the findings. The findings from this study may guide physicians to follow patients with AIT more closely by increasing awareness of risk factors.

— Ebru Sulanc, MD

ATA THYROID BROCHURE LINKS

Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/

HYPERTHYROIDISM, continued

ABBREVIATIONS & DEFINITIONS

Hyperthyroidism, thyrotoxicosis: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

Agranulocytosis: a marked decrease in the white blood cell count that causes a patient to be more likely to develop an infection. This is commonly associated with a fever and/or a sore throat.

White blood cells: the infection-fighting cells of the blood.

Iodine: an element found naturally in various foods that is important for making thyroid hormones and for normal thyroid function. Common foods high in iodine include iodized salt, dairy products, seafood and some breads.

Amiodarone: an iodine-rich drug that is commonly used for the treatment of irregular heart rhythms. Amiodarone can cause thyroid problems, including both hypothyroidism and hyperthyroidism

Amiodarone induced Thyrotoxicosis: elevated thyroid hormone levels that can occur as a result of excessive iodine from amiodarone resulting in increased thyroid hormone production and secretion or to destruction of thyroid cells with release of thyroid hormone into the blood

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HYPOTHYROIDISM

Thyroid surgery for patients with Hashimoto's disease

BACKGROUND

Hypothyroidism, or an underactive thyroid, is a common problem. In the United States, the most common cause of hypothyroidism is Hashimoto's thyroiditis. This is an autoimmune disorder where antibodies attack the thyroid, causing inflammation and destruction of the gland. Characteristic of Hashimoto's thyroiditis are high antibodies to thyroid peroxidase (TPO Ab) on blood tests. Hypothyroidism is treated by thyroid hormone and returning thyroid hormone levels to the normal range usually resolves symptoms in most patients.

However, in some patients, symptoms may persist despite what appears to be adequate treatment based on blood tests of thyroid function. This raises the possibility that some symptoms may be related to the autoimmune condition itself. Some studies suggest that TPOAb may cross-react with tissues other than the thyroid and may contribute to inflammation and general symptoms. Indeed, some patients with high TPOAb levels and normal thyroid hormone levels (without medication) will present with symptoms similar to those of patients with hypothyroidism. If persistent symptoms in patients with Hashimoto's thyroiditis are caused by the active autoimmune process rather than by thyroid hormone status, removing the thyroid gland through surgery may reduce the levels of the TPOAb and improve some symptoms. This study examines the effect of thyroidectomy compared to medical therapy for symptomatic hypothyroid patients with Hashimoto's thyroiditis despite achieving normal thyroid hormone levels after adequate thyroid hormone replacement.

THE FULL ARTICLE TITLE

Guldvog I et al Thyroidectomy versus medical management of euthyroid patients with Hashimoto's Disease and Persistent Symptoms: a randomized trial. Compared to Adequate Thyroid Hormone Replacement 2019 Annals of Internal Medicine. Epub 2019 Mar 12. PMID: 30856652.

SUMMARY OF THE STUDY

This study enrolled patients with hypothyroidism due to Hashimoto's thyroiditis who received treatment with thyroidectomy and thyroid hormone replacement or thyroid hormone replacement alone. The outcome of the study was a patient-reported health score on the generic Short Form-36 Health Survey (SF-36) after 18 months.

Patients were in the age group of 18 to 79 years. They all had a TPOAb titer >1000 IU/L and reported persistent symptoms despite having normal thyroid hormone levels based on blood tests. Typical symptoms included fatigue, increased need for sleep associated with reduced sleep quality, joint and muscle tenderness, dry mouth, and dry eyes. Follow up visits were done every 3 months for 18 months and the thyroid hormone therapy was adjusted as needed. After screening about 150 subjects were assigned to two groups

In the thyroidectomy and thyroid hormone replacement group, the health survey results improved 26 points and the average fatigue score decreased by 9 points. The thyroid hormone replacement only group had no significant change in either the health survey or the fatigue scores. After surgery, serum TPOAb levels declined sharply and significantly from a baseline of 2232 IU/ml to 152 IU/ml at 18 months, while levels declined only slightly in the thyroid hormone replacement-only group. Surgical complications included local postsurgical infections in 3 patients, prolonged low calcium levels in 3, and early postoperative hoarse voice quality which improved spontaneously or with therapy in 4.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that thyroidectomy in patients with Hashimoto's thyroiditis who had persistent thyroid-related symptoms on thyroid hormone replacement resulted in significantly higher health-related quality-of-life scores and lower fatigue scores as compared with continued thyroid

HYPOTHYROIDISM, continued

hormone therapy alone. Even though the results of this study indicate that surgical management of Hashimoto's thyroiditis may be beneficial, it is not clear whether undergoing surgery for this relatively common disease is necessary to treat symptoms in all patients. Also, patients had quite high levels of the TPO Antibody which may not be the case in all patients with Hashimoto's thyroiditis. Finally risk of surgical complications has to be taken into consideration. This study does, however, increase our awareness of the disease and tells us that surgical management of this condition should be considered. Certainly this study needs to be repeated and longer term studies in this area will certainly be of benefit.

—Vibhavasu Sharma, MD

ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Hashimoto's Thyroiditis: https://www.thyroid.org/hashimotos-thyroiditis/
Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/
Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/

ABBREVIATIONS & DEFINITIONS

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

Hashimotos thyroiditis: the most common cause of hypothyroidism in the United States. It is caused by antibodies that attack the thyroid and destroy it.

TPO antibodies (TPOAb): these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

Thyroid hormone therapy: patients with hypothyroidism are most often treated with Levothyroxine in order to return their thyroid hormone levels to normal. Replacement therapy means the goal is a TSH in the normal range and is the usual therapy. Suppressive therapy means that the goal is a TSH below the normal range and is used in thyroid cancer patients to prevent growth of any remaining cancer cells.

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THYROID CANCER

Are NIFTP tumors truly benign?

BACKGROUND

The incidence of thyroid cancer has been steadily rising, although the death rate from thyroid cancer has not changed. This is largely due to an increase in diagnosis of low-risk thyroid cancers. One such cancer is the encapsulated follicular variant papillary thyroid carcinoma. Outcomes for this cancer are particularly good and some feel that it may not even be a cancer at all, but rather a benign tumor. This has prompted recent work to rename this to "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). The incidence of NIFTP tumors has been reported to be between 16-23% and, when properly diagnosed using strict pathologic criteria, is felt to have a very favorable prognosis. However, the long-term effects of reclassifying this tumor have not been thoroughly studied. In the current study the authors reviewed thyroid cancer cases within a large tertiary care center to characterize the incidence of NIFTP tumors and to determine whether it is truly a benign tumor.

THE FULL ARTICLE TITLE

Parente DN et al 2018 Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly benign? World J Surg 42:321–326. PMID: 28828746.

SUMMARY OF THE STUDY

The authors reviewed all the pathology reports and specimens from all the patients who had surgery and were subsequently diagnosed with papillary thyroid cancer between December 2004 and February 2013 at a single, high volume academic center in North America. From these they identified 903 NIFTP tumors diagnosed using previously published criteria. The authors then applied even more rigorous criteria to these cases to identify a group of 102 (2.1%) "strictly diagnosed" NIFTP tumors. From these they calculated which of the NIFTP cases experienced an "adverse oncologic outcome" which they defined as patients whose cancer had spread to neck lymph nodes at the time of their initial treatment, as well as those whose cancer subsequently spread to neck lymph nodes or other organs in the body. They hypothesized that if NIFTP tumors were truly benign then very few patients would develop an adverse oncologic outcome.

Of the 102 cases that were analyzed, 77% were female and the average age was 48.6 years. Most (77.8%) were treated with a total thyroidectomy and 45 (44%) patients received radioactive iodine therapy. A total of 6 of the 102 patients (6%) had an adverse oncologic event (5 spread to neck lymph nodes and 1 to lungs).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The overall incidence of NIFTP tumors in this study was lower than expected; however, the small number of adverse oncologic events (6%) should not be dismissed by physicians. This study shows that, while NIFTP tumors have an excellent prognosis and do not need aggressive treatment after initial surgery, these patients still need to be monitored periodically for cancer recurrence.

— Phillip Segal, MD

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

THYROID CANCER, continued

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer: the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a new term has been used to describe a type of papillary thyroid cancer which is non-invasive. These cancers behave less aggressively than typical papillary thyroid cancer and have been shown to have low risk for recurrence and low risk for spread outside of the thyroid.

Follicular variant of papillary thyroid cancer: one of the subtypes of papillary thyroid carcinoma, which has been classified to three different forms: non-invasive follicular thyroid neoplasm with papillary-like nuclear features, invasive encapsulated and infiltrative FVPTC.

Thyroidectomy: surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When less is removed, such as in removal of a lobe, it is termed a partial thyroidectomy.

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

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HYPERTHYROIDISM

Thyroid antibody levels may not predict thyroid hormone levels and risk of recurrence in older patients with Graves' disease

BACKGROUND

Graves' disease is one of the most common causes of an overactive thyroid gland (hyperthyroidism). In Graves' disease, the patient's immune system produces high levels of antibodies to the TSH receptors (TRAb). TRAb then binds to the TSH receptor on the thyroid gland and stimulates it to increase thyroid hormone production. Graves' disease can be treated with antithyroid drugs (ATDs – Methimazole or PTU), radioactive iodine or surgery. ATDs can be used either in the short term to prepare patients for either radioactive iodine or surgery or as a long term treatment. When used as a long term treatment, the goal of ATDs is to cause the Graves' disease to go into remission, usually associated with the TRAb levels declining or going away. Once the ATDs are stopped, there can be anywhere from a 5-90% risk of relapse of the Graves' disease. Some of the risk factors that have been associated with increased risk of recurrence include: younger age, male sex, a large thyroid gland, severe hyperthyroidism at diagnosis, cigarette smoking and high TRAb levels at diagnosis or at the end of ATD treatment. This study was done to study possible association between the level of TRAb at diagnosis of Graves' disease and severity of hyperthyroidism and risk of recurrence after stopping ATD treatment.

THE FULL ARTICLE TITLE

Bano A et al 2019 Age May Influence the Impact of TRAbs on Thyroid Function and Relapse-Risk in Patients with Graves Disease. J Clin Endocrinol Metab 104(5):1378-1385.

SUMMARY OF THE STUDY

A total of 384 patients with Graves' disease (average age 48 years, 85.2% women, and 93.5% White) were included in the study from an endocrine clinic in England. All patients has thyroid levels and TRAb levels measured. If TRAb levels were not high, patients had a thyroid scan to confirm the diagnosis of Graves' disease. None of the patients in the study were taking other medications that can affect thyroid levels or were pregnant. A total of 231 patients were included in the study of risk of recurrence. Patient were treated with ATD for an average of 12 months. These patients were followed up to 12 months after stopping ATD treatment, with range of follow-up from 3 to 12 months.

A higher TRAb level at diagnosis was associated with higher thyroid hormone levels at diagnosis. This association was different in younger and older patients. In patients aged 55 years or older, a higher TRAb level was associated with higher thyroid hormone levels only if TRAb levels were below 10 U/L. In those with TRAb above 10 U/L, there was no association between TRAb level and thyroid hormone levels.

There was 5% increased risk of recurrence for every 1 unit increase in TRAb level at diagnosis in the whole group. Again, this association was different in younger and older patients. In patients aged 18-41 years, there was 13% increased risk of recurrence for every 1 unit increase in TRAb level at diagnosis. In patients aged 42-56 years, there was 5% increased risk of recurrence for every 1 unit increase in TRAb level at diagnosis. However, in patients aged 56 years or older, there was no association between TRAb level at diagnosis and risk of recurrence.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Higher TRAb levels at the diagnosis of Graves' disease were associated both with higher thyroid hormone levels at diagnosis and an increased risk of recurrence within 12 months of stopping ATD treatment in patients aged less than 55 years. In older patients with Graves' disease, TRAb level at diagnosis may not be a good marker of risk of recurrence. Therefore, decision on how often and how long to follow older patients after stopping ATD treatment for Graves' disease may be different than in younger patients.

— Sun Y. Lee, MD

HYPERTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Graves' Disease: https://www.thyroid.org/graves-disease/
Hyperthyroidism (Overactive): https://www.thyroid.org/hyperthyroidism/

ABBREVIATIONS & DEFINITIONS

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Thyroid scan: this imaging test uses a small amount of a radioactive substance, usually radioactive iodine, to obtain a picture of the thyroid gland.

TSH receptor: A molecule (protein) located on the thyroid cell surface that binds TSH and stimulates the production of the thyroid hormones within the thyroid cell.

TRAb: antibodies often present in the serum of patients with Graves disease that are directed against the TSH receptor, often causing stimulation of this receptor with resulting hyperthyroidism.

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

Thyroidectomy: surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When less is removed, such as in removal of a lobe, it is termed a partial thyroidectomy.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

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ATA Alliance for Thyroid Patient Education

GOAL The goal of our organizations is to provide accurate and reliable information for patients about the diagnosis, evaluation and treatment of thyroid diseases. We look forward to future collaborations and continuing to work together toward the improvement of thyroid education and resources for patients.

WHO WE ARE (in alphabetical order)

American Thyroid Association
www.thyroid.org
ATA Patient Resources:
www.thyroid.org/thyroid-information/
Find a Thyroid Specialist: www.thyroid.org
(Toll-free): 1-800-THYROID
thyroid@thyroid.org

Bite Me Cancer
www.bitemecancer.org
info@bitemecancer.org

Graves' Disease and Thyroid Foundation
www.gdatf.org
(Toll-free): 877-643-3123
info@ngdf.org

Light of Life Foundation
www.checkyourneck.com
info@checkyourneck.com

Thyca: Thyroid Cancer Survivors' Association, Inc.
www.thyca.org
(Toll-free): 877-588-7904
thyca@thyca.org

Thyroid Cancer Alliance
www.thyroidcanceralliance.org
www.thyroidcancerpatientinfo.org
Rotterdam, The Netherlands

Thyroid Cancer Canada
www.thyroidcancercanada.org
416-487-8267
info@thyroidcancercanada.org

Thyroid Federation International
www.thyroid-fed.org
tfi@thyroid-fed.org

AMERICAN THYROID ASSOCIATION
ATA | Founded 1923

Friends of the ATA

FOUNDED 2005

Get the latest thyroid health information. You'll be among the first to know the latest cutting-edge thyroid research that is important to you and your family.

Become a Friend of the ATA!
Subscribe to *Friends of the ATA e-news*

By subscribing to *Friends of the ATA Newsletter*, you will receive:

- *Friends of the ATA e-news*, providing up-to-date information on thyroid issues, summaries of recently published articles from the medical literature that covers the broad spectrum of thyroid disorders., and invitations to upcoming patient events
- Updates on the latest patient resources through the ATA website and elsewhere on the world wide web
- Special e-mail alerts about thyroid topics of special interest to you and your family

We will use your email address to send you *Friends of the ATA e-news* and occasional email updates. We won't share your email address with anyone, and you can unsubscribe at any time.

www.thyroid.org

AMERICAN THYROID ASSOCIATION
ATA | *Founded 1923*

Donate Now!

JOIN US

"The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information."

Mary Catherine Petermann
- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.

Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

Graves' Disease

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is located in the lower front of the neck. The thyroid makes thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormones help the body use energy, stay warm and keep the brain, heart, muscles, and other organs working appropriately.

WHAT IS GRAVES' DISEASE?

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (*hyperthyroidism*). It is the most common cause of hyperthyroidism in the United States. It is named after Robert Graves, an Irish physician, who described this form of hyperthyroidism about 150 years ago. It is 7-8 times more common in women than men.

WHAT CAUSES GRAVES' DISEASE?

Graves' disease is triggered by a process in the body's immune system, which normally protects us from foreign invaders such as bacteria and viruses. The immune system destroys foreign invaders with substances called antibodies produced by blood cells known as lymphocytes. Sometimes the immune system can be tricked into making antibodies that cross-react with proteins on our own cells. In many cases these antibodies can cause destruction of those cells. In Graves' disease these antibodies (called the thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) do the opposite – they cause the cells to work overtime. The antibodies in Graves' disease bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. This results in an overactive thyroid (*hyperthyroidism*).

WHAT ARE THE SYMPTOMS OF GRAVES' DISEASE?

- *Hyperthyroidism*

  The majority of symptoms of Graves' disease are caused by the excessive production of thyroid hormones by the thyroid gland (see *Hyperthyroidism brochure*). These may include, but are not limited to, racing heartbeat, hand tremors, trouble sleeping, weight loss, muscle weakness, neuropsychiatric symptoms and heat intolerance.

- *Eye disease*

  Graves' disease is the only kind of hyperthyroidism that can be associated with inflammation of the eyes, swelling of the tissues around the eyes and bulging of the eyes (called *Graves' ophthalmopathy or orbitopathy*). Overall, a third of patients with Graves' disease develop some signs and symptoms of Graves' eye disease but only 5% have moderate-to-severe inflammation of the eye tissues to cause serious or permanent vision trouble. Patients who have any suggestion of eye symptoms should seek an evaluation with an eye doctor (an ophthalmologist) as well as their endocrinologist.

  Eye symptoms most often begin about six months before or after the diagnosis of Graves' disease has been made. Seldom do eye problems occur long after the disease has been treated. In some patients with eye symptoms, hyperthyroidism never develops and, rarely, patients may be hypothyroid. The severity of the eye symptoms is not related to the severity of the hyperthyroidism.

  Early signs of trouble might be red or inflamed eyes, a bulging of the eyes due to inflammation of the tissues behind the eyeball or double vision. Diminished vision or double vision are rare problems that usually occur later, if at all. We do not know why, but problems with the eyes occur much more often and are more severe in people with Graves' disease who smoke cigarettes.

- *Skin disease*

  Rarely, patients with Graves' disease develop a lumpy reddish thickening of the skin in front of the shins known as pretibial myxedema (called Graves' dermopathy). This skin condition is usually painless and relatively mild, but it can be painful for some. Like the eye trouble of Graves' disease, the skin problem does not necessarily begin precisely when the hyperthyroidism starts. Its severity is not related to the level of thyroid hormone.

Graves' Disease

HOW IS THE DIAGNOSIS OF GRAVES' DISEASE MADE?

The diagnosis of hyperthyroidism is made on the basis of your symptoms and findings during a physical exam and it is confirmed by laboratory tests that measure the amount of thyroid hormones (thyroxine, or T4, and triiodothyronine, or T3) and thyroid-stimulating hormone (TSH) in your blood (see the *Hyperthyroidism brochure*). Clues that your hyperthyroidism is caused by Graves' disease are the presence of Graves' eye disease and/or dermopathy (see above), a symmetrically enlarged thyroid gland and a history of other family members with thyroid or other autoimmune problems, including type 1 diabetes, rheumatoid arthritis, pernicious anemia (due to lack of vitamin B12) or painless white patches on the skin known as vitiligo.

The choice of initial diagnostic testing depends on cost, availability and local expertise. Measurement of antibodies, such as TRAb or TSI, is cost effective and if positive, confirms the diagnosis of Graves' disease without further testing needed. If this test is negative (which can also occur in some patients with Graves' disease), or if this test is not available, then your doctor should refer you to have a radioactive iodine uptake test (RAIU) to confirm the diagnosis.

Also, in some patients, measurement of thyroidal blood flow with ultrasonography may be useful to establish the diagnosis if the above tests are not readily available.

HOW IS GRAVES' DISEASE TREATED?

The treatment of hyperthyroidism is described in detail in the *Hyperthyroidism brochure*. All hyperthyroid patients should be initially treated with beta-blockers. Treatment options to control Graves' disease hyperthyroidism include antithyroid drugs (generally methimazole [Tapazole®], although propylthiouracil [PTU] may be used in rare instances such as the first trimester of pregnancy), radioactive iodine and surgery.

Antithyroid medications are typically preferred in patients who have a high likelihood of remission (women, mild disease, small goiters, negative or low titer of antibodies). These medications do not cure Graves' hyperthyroidism, but when given in adequate doses are effective in controlling the hyperthyroidism.

If methimazole is chosen, it can be continued for 12-18 months and then discontinued if TSH and TRAb levels are normal at that time. If TRAb levels remain elevated, the chances of remission are much lower and prolonging treatment with antithyroid drugs is safe and may increase chances of remission. Long term treatment of hyperthyroidism with antithyroid drugs may be considered in selected cases.

If your hyperthyroidism due to Graves' disease persists after 6 months, then your doctor may recommend definitive treatment with either radioactive iodine or surgery.

If surgery (thyroidectomy) is selected as the treatment modality, the surgery should be performed by a skilled surgeon with expertise in thyroid surgery to reduce the risk of complications.

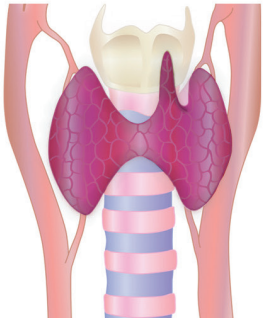
Your doctor should discuss each of the treatment options with you including the logistics, benefits and potential side effects, expected speed of recovery and costs. Although each treatment has its advantages and disadvantages, most patients will find one treatment plan that is right for them. Hyperthyroidism due to Graves' disease is, in general, controllable and safely treated and treatment is almost always successful.

WHAT WILL BE THE OUTCOME OF TREATMENT?

If you receive definitive treatment for your Graves' hyperthyroidism (such as radioactive iodine or surgery), you will eventually develop hypothyroidism (underactive thyroid). Even if you are treated with antithyroid drugs alone, hypothyroidism can still occur. Your doctor will check your *thyroid function tests* frequently to assess thyroid function following treatment. When hypothyroidism occurs, you will need to take a thyroid hormone tablet once a day at the right dose (see *Hypothyroidism brochure*).

OTHER FAMILY MEMBERS AT RISK

Graves' disease is an autoimmune disease and has a genetic predisposition. However, no specific gene has been identified for screening to date.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*