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# Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
*Optimal Thyroid Health for All*

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*Volume 16 | Issue 10 | October 2023*

# *Clinical Thyroidology® for the Public*



## 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 X (previously known as 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, MCT8 – AHDS Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International.*

We invite all of you to join our **Friends of the ATA** community. It is for you that the American Thyroid Association® (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. We thank all of the *Friends of the ATA* who support our mission and work throughout the year to support us. We invite you to help keep the ATA® mission strong by choosing to make a donation that suits you — it takes just one moment to give online at: www.thyroid.org/donate and all donations are put to good work. The ATA® is a 501(c)3 nonprofit organization and your gift is tax deductible.

**October is Thyroid Nodule Awareness Month.**

**In this issue, the studies ask the following questions:**

- What are patient's preferences in the management of indeterminate thyroid nodules?
- What was the effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules?
- Is NIFTP a cancer or not?
- What is the risk of hypothyroidism in babies born by women with active Graves' disease?
- Are different batches of levothyroxine consistently treating hypothyroidism?
- Is DTE becoming more popular to treat hypothyroidism?

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

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THYROID NODULES

# Dealing with indeterminate thyroid nodules in real life

## BACKGROUND

Thyroid nodules are fairly common, occurring in 30-50% of the adult population and the rate increases with age. It is important to identify which ones carry a risk for cancer, which occurs in 5-6% of nodules. Thus, the vast majority of nodules are benign (non-cancerous). Nodules are usually evaluated by ultrasound and concerning nodules are then biopsied. The biopsy results are reported using the Bethesda System which helps to determine the likelihood of cancer in the biopsied thyroid nodule. Bethesda I results means that there are not enough cells to make a diagnosis while Bethesda II results mean the nodule is benign. Bethesda V results are suspicious for cancer and Bethesda VI are positive for cancer. Bethesda III and IV results are called indeterminate, meaning that the cells are not entirely normal but not entirely abnormal. The likelihood of cancer increases going from Bethesda III to Bethesda IV. These nodules are either evaluated further with additional testing, monitored by ultrasound or referred to surgery.

Bethesda category III results are more common and include 2 categories: AUS - atypia of undetermined significance and FLUS — follicular lesion of undetermined significance. In these cases, it is important to evaluate and consider monitoring versus surgery. This study was done by a survey of patients, clinicians, and healthy patients with the goal to evaluate their preferences when addressing with Bethesda III thyroid nodules.

## THE FULL ARTICLE TITLE

van Kinschot CMJ et al 2023 Preferences of patients, clinicians, and healthy controls for the management of a Bethesda III thyroid nodule. Head Neck 45:1772–1781. PMID: 37158317.

## SUMMARY OF THE STUDY

Patients, clinicians, and healthy patients were added from hospitals in the Netherlands from August 2019 to July 2020. Those with a thyroid nodule were added to the study. The goal was to evaluate the effect of having a thyroid nodule and if ready to accept risks related to it. Those without a thyroid disease were added as healthy patients and clinicians who have treated patients with thyroid disorders were also added. All of participants were asked to imagine they have a thyroid nodule diagnosed with a Bethesda III category and to decide between surgery or monitoring.

The study evaluated 129 patients, 46 clinicians and 66 controls (healthy patients). Patients diagnosed with a thyroid nodule as well as the healthy patients were agreeable to accept a risk for thyroid cancer of <10.0% to monitor the nodule while a higher risk would rather have surgery while clinicians would accept a risk of < 15% to monitor the nodules. Patients also were ready to accept a risk of >15.5% for surgery in the future, which was similar to clinicians at 15.0% and 15.5% by healthy patients. When the patients with the thyroid nodule were offered surgery instead of monitoring, they were willing to accept a risk of >10.0%.

For the potential consequences, all groups agreed thyroid cancer risk as being the most important, followed by risk of permanent voice changes for clinicians and risk of more extensive surgery for patients with thyroid nodules and healthy patients. Interestingly, all groups rated the risk for hypothyroidism post-surgery as the least important risk.

## WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study explores the views of patients, clinicians, and healthy individuals on the management of Bethesda III thyroid nodules. These groups had similar viewpoints with regard to the risks of finding a thyroid cancer, of more extensive surgery, and of postoperative hypothyroidism. However, clinicians were less willing than patients to accept the risks of possible permanent voice changes.

— Joanna Miragaya, MD

## THYROID NODULES, continued

### ATA RESOURCES

Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/

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

### ABBREVIATIONS & DEFINITIONS

**Thyroid nodule:** an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

**Thyroid Ultrasound:** a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

**Thyroid biopsy:** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

**Bethesda System for Reporting Thyroid Cytopathology:** the scoring system used to evaluate thyroid biopsy results as to the risk of thyroid cancer.

**Indeterminate thyroid biopsy (Bethesda III):** this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

**Microcalcifications:** Small flecks of calcium within a thyroid nodule, usually seen as small bright spots on ultrasonography. These are frequently seen in nodules containing papillary thyroid cancer.

**Macrocalcifications:** Large flecks of calcium that can be seen either inside a thyroid nodule or in the periphery (so called egg-shell/rim calcifications), usually seen as large bright spots on ultrasonography.

**Molecular markers:** genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma™ Gene Expression Classifier and Thyroseq™

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THYROID NODULES

# Effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules

## BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of adults. The concern regarding thyroid nodules is whether the nodule is a cancer. The most common way to determine this is to do a biopsy of the nodule. About 5-6% of biopsies reveal papillary thyroid cancer and ~85% are benign (non-cancerous). However, 10-15% are called indeterminate, meaning the cells are not entirely normal but not entirely abnormal either. Sometimes, evaluating the cells for certain molecular markers that are seen in cancers can help determine whether surgery is needed. However, in areas that do not have access to molecular markers, surgery is usually recommended.

During the COVID-19 pandemic, many healthcare resources were diverted to focus on minimizing the spread of infectious diseases and on providing care to patients with COVID-19 infection. In this context, non-urgent and elective procedures for non-infectious diseases were often delayed. Worldwide, this resulted in delays in the diagnosis and treatment of many cancer types, including breast and colorectal cancers. However, the impact of such healthcare delays on more slow-growing cancers such as some thyroid cancer types, is unclear.

This study, which was focused on patients with a diagnosis of indeterminate thyroid nodules based on results of the thyroid biopsy, aimed to 1) determine to what extent thyroid surgery for indeterminate thyroid nodules was reduced during the COVID-19 pandemic; and 2) to determine whether or not the delay in thyroid surgery was associated with an increased occurrence of more aggressive thyroid cancer.

## THE FULL ARTICLE TITLE

Medas F et al 2023 Effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules (THYCOVID): A retrospective, international, multicentre, cross-sectional study. Lancet Diabetes 11:402–413. PMID: 37127041.

## SUMMARY OF THE STUDY

The study included data from 87,467 thyroid surgeries that took place at 157 centers in 49 countries. About one-quarter (22,974, 26%) of the thyroid surgeries were performed for a diagnosis of indeterminate thyroid nodules. The patients were divided into three groups: group 1 underwent thyroid surgery during the pre-pandemic phase (between January 1, 2019 and Feb 20, 2020), group 2 underwent thyroid surgery during the pandemic escalation phase (between March 1, 2020 and May 31, 2021), and group 3 underwent thyroid surgery during the pandemic decrease phase (between June 1, 2021 and December 31, 2021).

Analysis of the data found that there were relatively fewer thyroid surgeries performed during the pandemic escalation phase (group 2). Furthermore, compared to the pre-pandemic phase (group 1), there was an increase in the use of molecular testing as part of the evaluation of thyroid nodules prior to surgery during the pandemic decrease phase (group 3). Among the patients with indeterminate thyroid nodules who received thyroid surgery, there was an increase in the rate of thyroid cancer detected between group 1 and group 3 (39% in the pre-pandemic phase vs 42% in the pandemic escalation phase), and between group 2 and group 3 (39% in the pandemic escalation phase vs 42% in the pandemic decrease phase). Compared to the thyroid cancers that were diagnosed during the pre-pandemic phase (group 1), thyroid cancers diagnosed during the pandemic decrease phase (group 3) were larger in cancer size, more likely to have spread to lymph nodes, and associated with a higher risk of thyroid cancer recurrence.

## WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that surgery for indeterminate thyroid nodules decreased during the COVID-19 pandemic.

## THYROID NODULES, continued

In addition, the number of thyroid cancers at high risk for recurrence significantly increased the postpandemic period. Thus, the study findings suggest that thyroid surgery, when appropriate for the management of indeterminate thyroid nodules, should not be delayed.

— Debbie Chen, MD

### ATA RESOURCES

Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/

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

### ABBREVIATIONS & DEFINITIONS

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**Thyroid biopsy:** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

**Indeterminate thyroid biopsy:** this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

**Molecular markers:** genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma™ Gene Expression Classifier and Thyroseq™ 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).

**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*.

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THYROID NODULE

# Isolated NIFTP is a low-risk thyroid neoplasm

**BACKGROUND:**

Papillary thyroid cancer is the most common type of thyroid cancer and, overall, the prognosis is excellent. This is because papillary thyroid cancer grows very slowly and we have very effective treatments (surgery and, if needed, radioactive iodine). One type of papillary thyroid cancer, known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC), rarely spread outside of the thyroid. A study showed that no recurrence after surgery after at least 10 years of follow-up of 109 patients diagnosed with noninvasive encapsulated FVPTC.

In 2016, an international group of experts suggested that noninvasive encapsulated FVPTC was not a cancer at all and more consistent with a precancerous neoplasm (growth). They proposed to change the name to noninvasive thyroid follicular neoplasm with papillary-like nuclear features (NIFTP). The World Health Organization recognized NIFTP as a new term in 2017. The downgrade of the NIFTP category from carcinoma to a low-risk neoplasm was performed to reduce overtreatment of these tumors. The long-term outcome of NIFTP is still being investigated. The goal of this study was to analyze a large group of NIFTP patients diagnosed at a single institution since the introduction of this term in 2016 and further stratify and compare the pure NIFTP patients with those who had other co-existing low-risk and high-risk thyroid cancers.

**THE FULL ARTICLE TITLE:**

Alzumaili BA 2023 A Comprehensive Study on the Diagnosis and Management of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features. Thyroid 33:566–577. PMID: 36960710.

**SUMMARY OF THE STUDY:**

The study included 319 patients diagnosed with NIFTP between 2016 and 2022 identified through the Massachusetts General Hospital Laboratory Information database. The patients were divided into three groups: (1) NIFTP-only (183 patients); (2) NIFTP with one concomitant low risk papillary thyroid microcarcinoma (53 patients); and (3) NIFTP with a concomitant high risk thyroid carcinoma, defined as 2 or more microcarcinomas, any papillary thyroid carcinoma larger than 1.0 cm, any follicular or medullary thyroid carcinoma, or any thyroid cancer with spread to the neck lymph nodes (83 patients). In group 3, 15 (19%) patients with papillary thyroid cancer had spread to the neck lymph nodes.

Among all study patients, 73 patients (23%) had multiple thyroid nodules and 39 (12%) had multiple foci of NIFTP. A total of 256 (80%) of the thyroid nodules diagnosed as NIFTP after surgery underwent fine-needle aspiration (FNA) prior to the thyroid surgery with the following cytologic results: 12 patients (5%) non-diagnostic (Bethesda I), 34 patients (13%) benign (Bethesda II), 125 patients (49%) atypia of undetermined significance (Bethesda III), 43 patients (17%) follicular neoplasm (Bethesda IV), 32 patients (12%) suspicious for malignancy (Bethesda V), and 10 patients (4%) malignant (Bethesda VI). A total of 106 patients of the 114 patients who had molecular tests (93%) showed molecular alterations, the majority being RAS mutations (49 patients), with NRAS p.Q61R being the most common (32 patients).

Overall 66% of patients in group 1, 49% of patients in group 2, and 28% of patients in group 3 underwent a lobectomy. None of the patients who underwent initial lobectomy required treatment with completion thyroidectomy or radioactive iodine in group 1 and 2. In group 3, 6 out of 23 patients who underwent lobectomy required subsequent completion thyroidectomy, while 19 patients underwent radioactive iodine ablation. In group 1, follow-up neck ultrasound was performed in 28% of patients (52 patients). No recurrences or metastases were diagnosed within an average follow-up of 35 months (range 6–76 months) in group 1 and 45 months (range 8–77) in group 2. In group 3, 1 patient was diagnosed with neck lymph node cancer recurrence 8 months after surgery. All patients in group 3 were disease-free and there were no disease-specific deaths during an average follow-up of 46 months (range 6–77).

## THYROID NODULE, continued

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The results of this study evaluating a large group from a single medical center support the notion that isolated NIFTP is benign. The authors propose that patients with an isolated NIFTP should have clinical follow-up similar to a benign nodule and that the treatment of patients with NIFTP and concomitant thyroid cancers should be based on the non-NIFTP cancer. Additional long-term studies are needed to better define the best surgical approach and post-operative followup for patients diagnosed with NIFTP.

— Alina Gavrila, MD, MMSC

### ATA RESOURCES

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/
Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/
Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/
Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/

### ABBREVIATIONS & DEFINITIONS

**Thyroid carcinoma:** there are different types of thyroid cancer, with papillary thyroid carcinoma (PTC) being the most common followed by follicular thyroid carcinoma. Medullary thyroid carcinoma is a rare type of thyroid cancer that arises from the C-cells in the thyroid.

**Papillary microcarcinoma:** a papillary thyroid cancer smaller than 1 cm in diameter.

**Thyroid fine needle aspiration (FNA):** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

**The Bethesda System for Reporting Thyroid Cytopathology:** an international standardized reporting system with six cytologic categories, each category having a different cancer risk and specific recommendations for patient management. In addition to the non-diagnostic, benign and malignant categories, the Bethesda system includes three indeterminate categories for malignancy, which are subclassified as: (1) Atypia of undetermined significance (AUS); (2) Follicular neoplasm (FN) and (3) Suspicious for malignancy (SM). The indeterminate categories include specimens with adequate but abnormal cytology that have an increased risk of malignancy ranging between the benign and malignant categories that may require molecular testing for treatment decision.

**Molecular markers:** genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either diagnose cancer or to determine that the nodule is benign. The most common molecular marker tests are the Afirma™ Gene Expression Classifier, Thyroseq™ and ThyraMIR®.

**Mutation:** A permanent change in one of the genes.

**Cancer metastasis:** spread of the cancer from the initial organ where it developed to other organs, such as the lungs and bone.

**Lymph node:** bean-shaped organ that plays a role in removing what the body considers harmful, such as infections and cancer cells.

**Thyroidectomy:** surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a total thyroidectomy. When half of the thyroid removed, it is termed a hemithyroidectomy.

**Completion thyroidectomy:** surgery to remove the remaining thyroid lobe in thyroid cancer patients who initially had a lobectomy.

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HYPERTHYROIDISM

# Risk of hypothyroidism in babies born by women with active Graves' disease

## BACKGROUND

Graves' disease is a common cause of hyperthyroidism. It is an autoimmune disease in which the person makes antibodies (TSI or TRAb) that attack the thyroid gland, turning it on and causing an overactive thyroid. It is generally recommended that women with Graves' disease have normal thyroid function prior to becoming pregnant and be monitored closely during and after pregnancy. If they have active Graves' disease and hyperthyroidism during pregnancy, they are often treated with antithyroid medications such as methimazole or PTU to normalize their thyroid hormone levels. Women with active Graves' disease who become pregnant can pass both the antibodies and the antithyroid medications to the baby during pregnancy.

In general, the baby's thyroid hormone levels are often lower than those in the mother levels, so mothers are treated with the lowest dose of antithyroid drug to keep the free T4 level in the upper normal or just above the normal range for pregnancy. Overtreatment with antithyroid medications in the mother can lead to hypothyroidism in the baby. This is called neonatal hypothyroidism, as it resolves after the antithyroid medications get out of the baby's system after birth. The aim of this study was to determine how common neonatal hypothyroidism is in babies born to mothers with Graves' disease treated with antithyroid medications during pregnancy.

## THE FULL ARTICLE TITLE:

Yoshihara A et al 2023 Incidence of and risk factors for neonatal hypothyroidism among women with Graves' disease treated with antithyroid drugs until delivery. Thyroid. Epub 2023 Feb 21. PMID: 36680759

## SUMMARY OF THE STUDY:

This study is a study examining the pregnancy outcomes of women with Graves' diseases followed at a single hospital in Japan. They measured thyroid hormone (free T4) and TRAb levels and recorded antithyroid drug doses every 4-8 weeks during pregnancy and at the time of delivery. They assessed umbilical cord thyroid hormone levels at delivery to categorize neonatal thyroid status. They determined the incidence and predictors of neonatal hypothyroidism. A total of 305 mothers with Graves' disease that had been treated throughout pregnancy with antithyroid drugs and their babies were included in the study (63 treated with methimazole and 242 treated with PTU).

There were no significant differences in rates of neonatal hypothyroidism, defined as a low FreeT4 and high TSH in the umbilical cord blood sample, in babies born to mothers treated with methimazole (19%) compared to PTU (12.8%). Mothers of hypothyroid babies were more likely to have had higher thyroid hormone and TRAb levels than mothers of babies without hypothyroidism at birth, suggesting they had more active Graves' disease. Neonatal hypothyroidism is more commonly seen in babies born to women on higher doses of antithyroid drugs. Specifically, doses greater than 10 mg per day for methimazole and 150 mg per day for PTU were predictors of neonatal hypothyroidism. The authors recommended that mothers with active Graves' disease on antithyroid medications be followed closely during pregnancy with careful monitoring to optimize fetal health.

## WHAT ARE THE IMPLICATIONS OF THE STUDY?

Managing Graves' disease in women during pregnancy is complex and requires close monitoring of the mother and baby before and after delivery to reduce the risk of either hyper or hypothyroidism. Neonatal hypothyroidism was more common in babies born to mothers on higher antithyroid medication doses with more active Graves disease. Mothers and their babies should be closely monitored during pregnancy and after delivery to ensure normal thyroid function in both.

— Whitney Woodmansee, MD

## HYPERTHYROIDISM, continued

### ATA RESOURCES

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

### ABBREVIATIONS & DEFINITIONS:

**Graves' disease:** the most common cause of hyperthyroidism in the United States. It is caused by antibodies (TSI or TRAb) 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.

**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.

**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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THYROID HORMONE REPLACEMENT

# Are different batches of levothyroxine consistently treating hypothyroidism?

## BACKGROUND

Hypothyroidism, or underactivity of the thyroid gland, comes in 2 general forms: primary hypothyroidism (high TSH and low T4) and secondary hypothyroidism (low/normal TSH, low T4 and T3). Primary hypothyroidism is most commonly caused by an autoimmune thyroid disease called Hashimoto's thyroiditis which causes destruction of the thyroid gland. Primary hypothyroidism can also be caused by pregnancy, minor illnesses, lithium, surgery, and some medications like tyrosine kinase inhibitors used to treat thyroid and other cancers. Secondary hypothyroidism occurs when the pituitary gland in the head cannot send the thyroid gland in the neck enough TSH.

This study was done to see if TSH levels that are monitored during the treatment of both types of hypothyroidism are significantly changed when switching to/from generic or brand name formulations of levothyroxine hormone replacement therapy. This study is challenging because of weight, absorption, compliance, and medication interaction changes that might alter TSH values regardless of the medication itself. The goal of this study is to look at the frequency of normal TSH values and likelihood of abnormal TSH values when different levothyroxine preparations are taken.

## THE FULL ARTICLE TITLE

Bianco AC et al Levothyroxine Treatment Adequacy and Formulation Changes in Patients With Hypothyroidism: A Retrospective Study of Real-World Data From the United States Thyroid, 2023, online.

## SUMMARY OF THE STUDY

Patients diagnosed with either primary or secondary hypothyroidism between the years of 2013 and 2020 were randomly chosen from a medical database. Patients were chosen mostly from the clinic setting with at least two TSH values spaced at least 1-15 months apart were included, and those who switched levothyroxine formulations were identified.

Out of a total 11,259 patients, 81.1% of these patients had a normal TSH for their first measurement. Subsequently, 24.9% of these patients had at least one formulation change for their levothyroxine prescription. These patients were matched by age, sex, and insurance type and still greater than 70% had a normal TSH at the second (follow up) measurement in these matched categories. However, 11.7% of the patients had a moderately high TSH, meaning the levothyroxine dose was too low. In addition, 7.3% of the patients had a moderately low TSH, meaning the levothyroxine dose was too high. Only 4% of the patients had very low TSH values below 0.1mIU/L or very high TSH values above 10 mIU/L.

## WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Most hypothyroid patients (81.1%) have a normal TSH on their levothyroxine medication, despite 24.9% of these patients having at least one formulation change (whether in between generic or brand name). This suggests that a change from generic to brand levothyroxine or vice versa does not significantly change TSH levels. Importantly, this study did not include any clinical symptoms associated with the change in levothyroxine formulations, so that cannot be evaluated. However, this study is helpful to show that the majority of patients with a normal TSH on one levothyroxine formulation will have a normal TSH on another formulation.

— Pinar Smith, MD

## THYROID HORMONE REPLACEMENT, continued

### ATA RESOURCES

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

### ABBREVIATIONS & DEFINITIONS

**Autoimmune thyroid disease:** a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

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

**Primary hypothyroidism:** the most common cause of hypothyroidism cause by failure of the thyroid grand.

**Secondary hypothyroidism:** a rare cause of hypothyroidism where the thyroid gland is normal and the problem is inadequate TSH secretion from the pituitary gland.

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

**Pituitary gland:** this endocrine gland sits at the base of the brain and secretes hormones that control thyroid and adrenal function, growth and reproduction. The pituitary gland secretes TSH to control thyroid function.

**Levothyroxine (T4):** the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tyrosint™ and generic preparations.

**TSH: thyroid stimulating hormone —** produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

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HYPOTHYROIDISM

# Increase in DTE prescriptions in the United States for the treatment of hypothyroidism

## BACKGROUND

Hypothyroidism, or underactive thyroid, is diagnosed with a higher TSH and low or low-normal FT4. Common symptoms include feeling tired, cold, constipated, gaining weights and having dry skin. Hypothyroidism is most often treated with levothyroxine, which is the main hormone that the normal thyroid makes (T4). Levothyroxine is then converted in the body, to the active thyroid hormone, triiodothyronine (T3).

Another thyroid hormone preparation is desiccated thyroid extract (DTE), which was the main treatment for hypothyroidism before levothyroxine was isolated and purified in the 1960s. DTE has both forms of thyroid hormone as it is made by ground up thyroids from either cows or pigs. As such, it contains both T4 and T3. Some practitioners and some patients prefer DTE because of it containing bother thyroid hormones. Further, some patients that do not feel well on levothyroxine alone do better on DTE.

A third thyroid hormone preparation is T3, or liothyronine. This is usually used along with levothyroxine (T4/T3 therapy).

This study reviewed clinical prescriptions databases regarding prescriptions for levothyroxine and desiccated thyroid extract to understand the frequency of prescriptions of these forms of thyroid hormone replacement.

## THE FULL ARTICLE TITLE

Ettleson MD et al 2023 Demographic, healthcare access, and dietary factors associated with thyroid hormone treatments for hypothyroidism. J Clin Endocrinol Metab. Epub 2023 Jun 16. PMID: 37327351.

## SUMMARY OF THE STUDY

This study reviewed two databases for thyroid hormone prescriptions. Data was reviewed for those patients who had received at least one new thyroid hormone prescription for a diagnosis of hypothyroidism. The years of study were 1996 to 2020 among the two databases. A total of 524,818 patients were included. The average age was 50.8 years, and 72.1% were women.

On an average annual basis, there were 47,711 adults who received at least 1 new thyroid hormone prescription—88.3% levothyroxine, 2.0% liothyronine, and 9.4% DTE therapy. The proportion of newly prescribed DTE therapy increased from 5.4% in 2010 to 10.2% in 2020. New liothyronine prescriptions remained relatively stable between the two periods—2.4% in 2010 and 2.2% in 2020. Regions with many PCP and endocrinology physicians were associated with increased use of levothyroxine. The proportion of DTE or liothyronine use was higher in the West and Southwest U.S. regions than in the North and upper Midwest regions. Liothyronine and DTE therapies were more common in patients living in large metropolitan zones than in those living in rural zones Conversely, levothyroxine was less likely to be prescribed in metropolitan zones than in in rural zones.

## WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study showed that the prescriptions for desiccated thyroid extract have doubled between the years 2010 and 2020. There has been a notable increase in the percentage of prescriptions for DTE. Even though it averages to about 10% of the total prescriptions of thyroid hormone, the use has increased, especially in areas with a low number of physicians and large metropolitan areas. It would be important to educate patients on the differences between various thyroid hormone preparations so they can make an informed decision. Understanding the risks such as side effects versus benefits of the DTE preparations is important as well.

—Vibhavasu Sharma,MD,FACE

## HYPOTHYROIDISM, continued

### ATA RESOURCES

Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/

### ABBREVIATIONS & DEFINITIONS

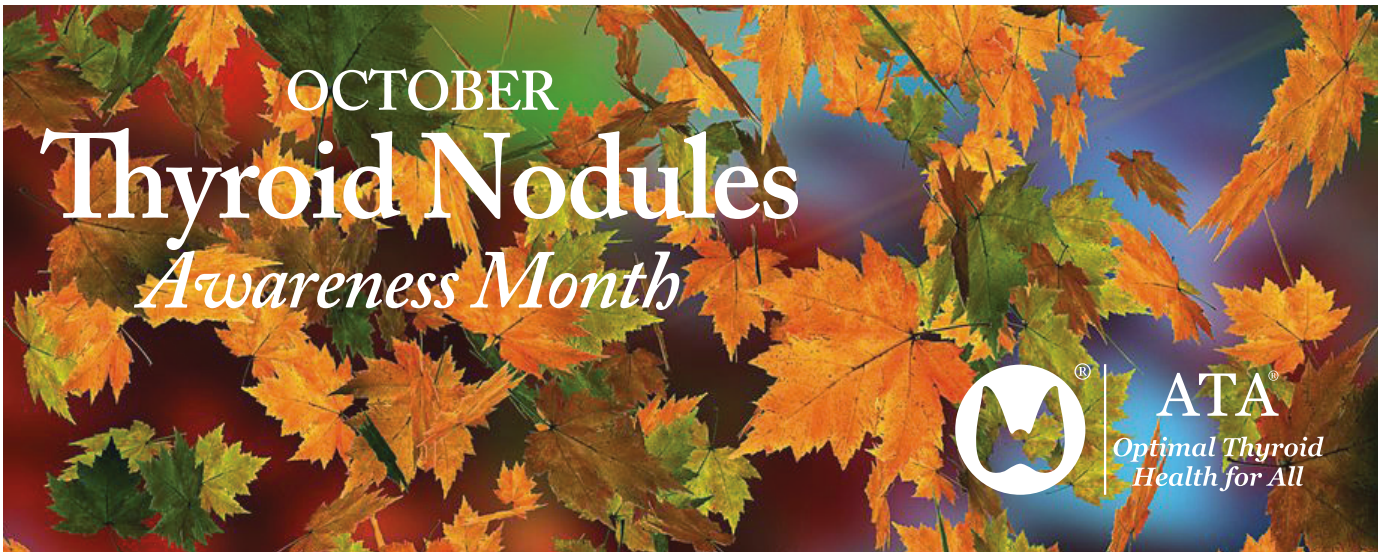
**Hypothyroidism:** a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

**Levothyroxine (T4):** the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tyrosint™ and generic preparations.

**Desiccated thyroid extract (DTE):** thyroid hormone pill made from animal thyroid glands. Currently desiccated thyroid extract is made from pig thyroids and is available as Armour Thyroid™ and Nature-Throid™.

**Thyroxine (T4):** the major hormone produced by the thyroid gland. T4 gets converted to the active hormone T3 in various tissues in the body.

**Triiodothyronine (T3):** the active thyroid hormone, usually produced from thyroxine. Available in pill form as liothyronine or Cytomel™.



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**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.

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### Graves' Disease and Thyroid Foundation
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info@ngdf.org

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

### MCT8 – AHDS Foundation
**mct8.info**
Contact@mct8.info

### Thyca: Thyroid Cancer Survivors' Association, Inc.
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thyca@thyca.org

### Thyroid Cancer Alliance
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**www.thyroidcancerpatientinfo.org**
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### Thyroid Cancer Canada
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