

# Clinical Thyroidology<sup>®</sup> for the Public



AMERICAN THYROID ASSOCIATION  
Optimal Thyroid Health for All



## EDITOR'S COMMENTS .....2

### HYPOTHYROIDISM .....3

#### Why do so many patients receiving levothyroxine treatment for hypothyroidism have persistent symptoms?

In the majority of patients with hypothyroidism, symptoms either improve or resolve when thyroid hormone levels are returned to the normal range with thyroid hormone therapy. However, some patients might still have some symptoms despite thyroid levels being normalized. This study analyzed how many have new or persistent symptoms after the use of levothyroxine to treat hypothyroidism.

Hidalgo J et al 2023 Real practice assessment of persistent symptoms after initiation of levothyroxine. *Endocr Pract.* Epub 2023 Oct 30:S1530-891(23)00730-9. PMID: 37913925.

### THYROID AND PREGNANCY .....5

#### Levothyroxine treatment of subclinical hypothyroidism in pregnancy did not improve brain development testing scores in children up to 2 years of age.

Thyroid hormone plays an important role in baby's development during pregnancy. Guidelines agree that overt hypothyroidism in pregnancy should be treated. However, it is less clear whether subclinical hypothyroidism in pregnancy should be treated because studies have not yet shown clear benefit in treating with levothyroxine. The researchers of this study aimed to evaluate potential benefit of levothyroxine treatment of overt and subclinical hypothyroidism during pregnancy on the child's subsequent brain development.

Zhao Z et al 2023 Impact of levothyroxine therapy for maternal subclinical and overt hypothyroidism on early child neurodevelopment: A prospective cohort study. *Clin Endocrinol (Oxf).* Epub 2023 Oct 20. PMID: 37859522

### HYPOTHYROIDISM .....7

#### TSH spontaneously normalizes in many older adults with subclinical hypothyroidism

Subclinical hypothyroidism is a mild form of hypothyroidism defined by TSH levels above the normal range and normal thyroid hormone levels in the blood. However, sometimes mildly elevated TSH levels normalize after a few months. This study was done to better understand how common this normalization occurs, and which patients are more likely to normalize.

Van der Spoel E et al 2023 Incidence and determinants of spontaneous normalization of subclinical hypothyroidism in older adults. *J Clin Endocrinol Metab.* Epub 2023 Oct 20:dgad623. PMID: 37862463.

## THYROID NODULE .....9

#### Unnecessary surgery is performed in the majority of indeterminate cytology thyroid nodules managed without molecular testing

About 15-20% of thyroid biopsies fall into the indeterminate category, meaning that the cells obtained by the biopsy are not entirely normal nor abnormal. One of the main advantages of molecular testing in indeterminate thyroid nodules is the possibility of reducing the use of unnecessary thyroid surgery to make a diagnosis. The authors of this study aimed to evaluate the frequency of unnecessary thyroid surgery for indeterminate nodules without the aid of molecular tests in Europe.

Mavromati M et al. Unnecessary thyroid surgery rate for suspicious nodule in the absence of molecular testing. *Eur Thyroid J.* 2023;12(6):e230114; doi: 10.1530/ETJ-23-0114. PMID: 37855426.

## THYROID CANCER.....11

#### Is a lobectomy a treatment option for papillary thyroid cancer when thyroid nodules remain in the opposite lobe after surgery?

Treatment for papillary thyroid cancer with a thyroid lobectomy is becoming more common. However, a major disadvantage of lobectomy is that the remaining thyroid not removed during surgery may also contain or, at some point may form, another papillary thyroid cancer, especially if nodules are already present in this remaining thyroid tissue. The authors study the risk of papillary thyroid cancer being present, or developing over time, for people who underwent thyroid lobectomy for treatment of papillary thyroid cancer.

Pak SJ et al Contralateral low-to-intermediate suspicion nodule is not a contraindication for lobectomy in patients with papillary thyroid carcinoma. *Thyroid.* Epub 2023 Aug 25. PMID: 37624735

## HYPOTHYROIDISM .....13

#### Safety of levothyroxine plus liothyronine (T4/T3) therapy in postsurgical hypothyroidism

While the standard of care for treatment of hypothyroidism is levothyroxine, some patients have continued symptoms while on levothyroxine alone. Because of this, some have tried a combination of levothyroxine and liothyronine (T4/T3 therapy) to try to treat continue symptoms on levothyroxine alone in patients with postsurgical hypothyroidism. In this study, investigators evaluated the effects of T4/T3 therapy on heart function parameters in healthy patients that have undergone thyroidectomy for thyroid cancer.

Biondi B et al. Preliminary results of a double-blind randomized controlled trial evaluating the cardiometabolic effects of levothyroxine and liothyronine compared to levothyroxine with placebo in athyreotic low-risk thyroid cancer patients. *Thyroid.* 2023;33(12):1402-1413; doi: 10.1089/thy.2023.0135. PMID: 37725587.



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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 X (previously known as Twitter) at [@thyroidfriends](https://twitter.com/thyroidfriends) and on [Facebook](https://www.facebook.com/thyroidfriends). 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 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](http://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.

**March is [Medullary Thyroid Cancer Awareness Month](#).**

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

- Why do so many hypothyroid patients on levothyroxine have persistent symptoms?
- Does levothyroxine replacement in subclinical hypothyroidism during pregnancy affect brain development?
- How often does subclinical hypothyroidism in older adults resolve?
- How often do patients with benign nodules but indeterminate cytology undergo surgery if molecular markers are not available?
- Is a lobectomy a treatment option for papillary thyroid cancer when thyroid nodules remain in the opposite lobe after surgery?
- Is T4/T3 combination therapy safe to use in postsurgical 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



## HYPOTHYROIDISM

### Why do so many patients receiving levothyroxine treatment for hypothyroidism have persistent symptoms?

#### BACKGROUND

Hypothyroidism, a condition that results in an underactive thyroid, is very common. Overt hypothyroidism occurs when both the TSH level is high and the FT4 levels is low. Subclinical hypothyroidism occurs when the TSH is increased but the FT4 level is normal. Treatment of hypothyroidism is thyroid hormone replacement, usually in the form of levothyroxine.

Symptoms of hypothyroidism may include being tired, slow, sluggish, gaining weight, cold, dry skin and constipation. None of these symptoms are specific to hypothyroidism. In the vast majority of patients with overt hypothyroidism, symptoms either improve or resolve when thyroid hormone levels are returned to the normal range with thyroid hormone therapy. In patients with subclinical hypothyroidism, results are not as clear. Indeed, in both overt and subclinical hypothyroidism, some patients might still have some symptoms despite thyroid levels being normalized. This study analyzed how many have new or persistent symptoms after the use of levothyroxine to treat hypothyroidism.

#### THE FULL ARTICLE TITLE

Hidalgo J et al 2023 Real practice assessment of persistent symptoms after initiation of levothyroxine. *Endocr Pract.* Epub 2023 Oct 30;S1530-891(23)00730-9. PMID: 37913925.

#### SUMMARY OF THE STUDY

The study analyzed random 500 patient charts between January 2017 and December 2019 at a single center (Mayo Clinic in Rochester, Minnesota, U.S.A). Included patients' charts had at least one follow up note after levothyroxine initiation and up to 3 more with labs and documented symptoms. Results showed 356 patients, 66.6% being female, white (92.3%), and having obesity

(71.9%). Several other disorders were commonly noted in 72.7%, with depression being the leading one common in 35.3% of all. At the initial visit, almost half of the patients (47.7%) had symptoms consistent with hypothyroidism, with fatigue being the most common. More than half of those patients were started on levothyroxine therapy for subclinical hypothyroidism. The average initial dose of levothyroxine prescribed was 50 mcg. Despite starting patients on levothyroxine, around 40% of the patients still had laboratory numbers indicating subclinical hypothyroidism, even during the follow-up period.

During the first, second, and third follow-up encounters, 26.7% (42 of 157), 27.3% (29 of 106), and 28% (16 of 57) of patients experienced persistent or new symptoms of hypothyroidism, despite normalized TSH values. Fatigue remained the most common symptoms, followed by weight gain. The treating physician chose to increase the levothyroxine dose in about 20% of patients, referred to an endocrinologist in 2.2% of patients at the first follow-up visit (and in 17.6% by the third encounter), and suggested other strategies (e.g., rheumatology referral, psychological or nutrition counseling) in 6.7% of patients at the first and second encounter and in 11.8% at the third evaluation.

#### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that ~1 in 4 patients with hypothyroidism on levothyroxine still reports symptoms, despite normal TSH levels. Whether these symptoms were due to hypothyroidism or to other disorders is unclear. Although the authors did not identify causes for it, this study shows the need to better understand the issue in order to help with solutions for our patients and to not overlook their symptoms.

— Joanna Miragaya, MD



## HYPOTHYROIDISM, continued

### ATA RESOURCES

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

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

**Subclinical Hypothyroidism:** a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

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

**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.

**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.



## THYROID AND PREGNANCY

# Levothyroxine treatment of subclinical hypothyroidism in pregnancy did not improve brain development testing scores in children up to 2 years of age.

### BACKGROUND

Thyroid hormone plays an important role in baby's development during pregnancy. In particular, brain development is very sensitive to thyroid hormones. Because the baby's thyroid gland does not start making thyroid hormone until 18-20 weeks of pregnancy, it is especially important for pregnant women to have adequate thyroid hormone available during critical period of development in early pregnancy. Several studies have suggested that low thyroid hormone levels (hypothyroidism) in the mother during pregnancy may cause problems with the baby's brain development.

Hypothyroidism can be either overt hypothyroidism (high thyroid stimulating hormone (TSH) and low thyroxine (free T4 levels) or subclinical hypothyroidism (a milder form of hypothyroidism with high TSH and normal free T4 levels). Guidelines agree that overt hypothyroidism in pregnancy should be treated with levothyroxine to prevent adverse impact on the health of the mother and the baby's development. However, it is less clear whether subclinical hypothyroidism in pregnancy should be treated because studies have not yet shown clear benefit in treating with levothyroxine. The researchers of this study aimed to evaluate potential benefit of levothyroxine treatment of overt and subclinical hypothyroidism during pregnancy on the child's subsequent brain development.

### THE FULL ARTICLE TITLE

Zhao Z et al 2023 Impact of levothyroxine therapy for maternal subclinical and overt hypothyroidism on early child neurodevelopment: A prospective cohort study. Clin Endocrinol (Oxf). Epub 2023 Oct 20. PMID: 37859522

### SUMMARY OF THE STUDY

A total of 442 pregnant patients before 16 weeks of singleton pregnancy seen at Fudan University hospital in China between January 1, 2012 and December 31,

2013 participated in the study. Patients were divided into either overt or subclinical hypothyroidism group based on normal ranges recommend by the 2011 American Thyroid Association guidelines. Decision for treatment with levothyroxine was made by patient's individual endocrinologists. Children of these women were tested at 1, 3, 6, 12, and 24 months of age using a Gesell Development Diagnosis Scale. The scores were used to compare brain status between children born to mothers with subclinical hypothyroidism (SCH group) and those born to mother with overt hypothyroidism (OH group).

Pregnant patients in SCH group were tested for thyroid levels later than those in OH group on average (13.6 weeks vs. 8 weeks of pregnancy). About two-thirds (61%) of patients in OH group were already diagnosed with hypothyroidism before becoming pregnant. On the other hand, 90% of patients in SCH group were diagnosed during pregnancy. On average, patients in SCH group were started on levothyroxine 2 weeks later than patients in OH group. However, most of patients in both groups were taking levothyroxine by the end of pregnancy (99.4% patients in SCH group and 100% in OH group).

Children in SCH group had lower scores in five areas of tests compared to children in OH group: gross motor and social-emotional responses at 3 months, adaptability at 6 months (average score of 98 vs 103), gross motor skills at 1 year (average score of 102.54 vs 104.64), and language skills at 2 years (average score of 106.2 vs 112.64).

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors concluded that children born to mother with subclinical hypothyroidism had lower scores on brain developmental testing compared to those born to mothers with overt hypothyroidism in the first 2 years of life. This finding may be due to differences in when levo-



## THYROID AND PREGNANCY, continued

thyroxine treatment started. Many of women with overt hypothyroidism were already diagnosed and started on treatment before becoming pregnant while most women with subclinical hypothyroidism were diagnosed during pregnancy. Therefore, the results of this study suggest that early treatment of hypothyroidism in pregnancy is especially important to benefit developing baby's brain. A

larger study with comparison group of children born to mothers without thyroid disease and treatment initiation at earlier in pregnancy would be needed to better understand potential benefit of levothyroxine treatment of subclinical hypothyroidism in pregnancy.

— Sun Y. Lee, MD, MSc

### ATA RESOURCES

Thyroid Disease in Pregnancy: <https://www.thyroid.org/thyroid-disease-pregnancy/>

### ABBREVIATIONS & DEFINITIONS

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

**Subclinical Hypothyroidism:** a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

**Overt Hypothyroidism:** clear hypothyroidism an increased TSH and a decreased T4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

**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.

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

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



## HYPOTHYROIDISM

# TSH spontaneously normalizes in many older adults with subclinical hypothyroidism

### BACKGROUND

Subclinical hypothyroidism is a mild form of hypothyroidism defined by TSH levels above the normal range and normal thyroid hormone (FT4) levels in the blood. TSH is a pituitary hormone that is very sensitive to changes in thyroid hormone levels. In the early stages of hypothyroidism, TSH levels increase before the thyroid levels become low. However, sometimes mildly elevated TSH levels normalize after a few months. This study was done to better understand how common this normalization occurs, and which patients are more likely to normalize.

### THE FULL ARTICLE TITLE

Van der Spoel E et al 2023 Incidence and determinants of spontaneous normalization of subclinical hypothyroidism in older adults. *J Clin Endocrinol Metab*. Epub 2023 Oct 20;dgad623. PMID: 37862463.

### SUMMARY OF THE STUDY

This study looked at individuals older than 65 years old from four different European countries (UK, Netherlands, Switzerland and Ireland). At the beginning of the study all the patients had mildly elevated TSH levels: 4.6-19.9 mIU/L and normal FT4 levels. The study looked at TSH over time.

The authors studied two groups of patients: the first group (2335 patients) had one single elevated TSH value at the beginning of the study and a repeat test at one year. Their average age was 72, 60% were women and their average TSH level was 5.4. The second group (361 patients) had

two abnormal TSH levels tested about three months apart, confirming persistent subclinical hypothyroidism, and a third TSH level tested after 1 year. Their average age was 75, 52% were women and the average TSH level was 5.75. None of these patients received treatment with thyroid hormone.

In the first group, 60% of the patients had normal TSH levels when retested at one year. This was even more common among younger patients, female patients and those who had lower initial TSH and higher FT4 levels. TSH normalization was also more common if the second measurement was done in the summer months. In the second group, 40% of the patients had normal TSH levels at one year. The patients most likely to have normal TSH levels at one year were younger, female, had initial lower TSH and higher Ft4 levels and had negative TPO (thyroid peroxidase antibodies).

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that, among people older than 65 years old, TSH levels in the subclinical hypothyroid range commonly normalize over time without treatment. Clinicians should measure TSH levels at least twice before recommending treatment. In addition, a third TSH measurement over time, particularly for those patients who are most likely to normalize, such as women and those with minimal TSH elevations, may be helpful in order to avoid unnecessary treatment.

— Susana Ebner MD

### ATA RESOURCES

Older Patients and Thyroid Disease: <https://www.thyroid.org/thyroid-disease-older-patient/>

Thyroid Function Tests: <https://www.thyroid.org/thyroid-function-tests/>

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



## HYPOTHYROIDISM, continued

### ABBREVIATIONS & DEFINITIONS

**Subclinical Hypothyroidism:** a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

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

**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.

**TPO antibodies:** 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.



AMERICAN THYROID ASSOCIATION  
Optimal Thyroid Health for All

MARCH

# Medullary Thyroid Cancer *Awareness Month*





## THYROID NODULE

# Unnecessary surgery is performed in the majority of indeterminate cytology thyroid nodules managed without molecular testing

### BACKGROUND

Thyroid nodules are very common and may be found in up to 50% of individuals that have imaging of the neck. The concern of a thyroid nodule is whether it is a cancer. Fortunately, only 5-6% of nodules are cancerous. Evaluation of a thyroid nodule includes an ultrasound to characterize the nodule as to the risk of cancer followed by a thyroid biopsy of the higher risk nodules to make a diagnosis. About 15-20% of thyroid biopsies fall into the indeterminate category, meaning that the cells obtained by the biopsy are not entirely normal nor abnormal. Prior to the development of molecular marker testing, the only way to make a diagnosis in an indeterminate nodule was surgery to remove the nodule. This meant that many benign nodules were removed by surgery.

The major breakthrough to identify which indeterminate nodules are benign and do not require surgery was the development of molecular marker analysis on biopsy specimens. Molecular markers test for genes that are associated with cancer. If molecular marker testing is negative, the nodule is considered benign and does not require surgery. Thus, one of the main advantages of molecular testing in indeterminate thyroid nodules is the possibility of reducing the use of unnecessary thyroid surgery to make a diagnosis. However, these tests are costly and not widely available, particularly in Europe, and their cost-effectiveness has been challenged. The authors of this study aimed to evaluate the frequency of unnecessary thyroid surgery for indeterminate nodules without the aid of molecular tests in Europe.

### THE FULL ARTICLE TITLE

Mavromati M et al. Unnecessary thyroid surgery rate for suspicious nodule in the absence of molecular testing. *Eur Thyroid J.* 2023;12(6):e230114; doi: 10.1530/ETJ-23-0114. PMID: 37855426.

### SUMMARY OF THE STUDY

This was a single-center study of consecutive patients undergoing thyroid biopsy under ultrasound guidance between January 2017 and December 2021 in the endocrinology and radiology division of Geneva University Hospital. The European Thyroid Imaging and Reporting Data System (EU-TIRADS) score and the Bethesda System for Reporting Thyroid Cytopathology were assessed. Patients were referred to surgery if the patient have symptoms or if results were indeterminate or cancer. Unnecessary surgery was defined as benign pathology after initial surgery for a nodule with indeterminate cytology in the absence of local compressive symptoms. Indeterminate categories were Bethesda 3 (Atypia of Unknown Significance, AUS), Bethesda 4 (Follicular Neoplasm, FN) and Bethesda 5 (Suspicious for Malignancy, SFM). Descriptive analysis was performed, and the association between EU-TIRADS score and rate of cancer in indeterminate nodules was evaluated.

Out of 1010 nodules in 862 patients (average age, 54.2 years), 1189 biopsies were performed. EU-TIRADS indeterminate scores 3 (33.5%) and 4 (41.9%) were the most frequent ultrasound findings. Surgery was indicated in 33.3% of all patients, and 56.8% underwent lobectomy. According to cytology, 36% of all AUS, 74% of all FN, and 97% of all SFM nodules were referred for surgery. For AUS, FN, and SFM nodules, the benign rate was 81%, 76%, and 21%, respectively. Combining the EU-TIRADS score with the Bethesda classification did not yield a significantly higher cancer rate. Surgery was considered unnecessary in 56%, 68%, and 21% of patients with Bethesda 3, 4, and 5.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study confirms that the majority of nodules with indeterminate cytology are indeed benign. What is not



## THYROID NODULE, continued

known is how many of the benign nodules with indeterminate cytology would also have negative molecular markers. However, it is likely that many of the benign nodules would also have negative molecular marker analysis. In this study, 56 to 68% of nodules with AUS/FN cytology and 21% with SFM cytology did not

harbor cancer. These cases reveal the real-life number of unnecessary thyroidectomies in indeterminate nodules and provides that case for more widespread use of molecular marker analysis.

— Alan P. Farwell, 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/>

### 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.

**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™

**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.



## THYROID CANCER

# Is a lobectomy a treatment option for papillary thyroid cancer when thyroid nodules remain in the opposite lobe after surgery?

### BACKGROUND

The formation of abnormal growths in the thyroid gland, a butterfly-shaped organ in the front part of the neck that produces thyroid hormone, is very common. These growths, called nodules, frequently develop in both sides of the gland (in both 'wings' of the butterfly-shaped thyroid). Most of the time, thyroid nodules are benign (non-cancerous), although a small fraction will turn out to be cancerous. The most common type of thyroid cancer is called papillary thyroid cancer and this type of cancer has an excellent prognosis. Treatment for papillary thyroid cancer usually requires thyroid surgery, which may involve removing only that part of the thyroid in which the cancer is discovered (called a thyroid lobectomy) or removing the entire thyroid gland (called a total thyroidectomy).

A thyroid lobectomy has several advantages compared to total thyroidectomy. First, the non-cancerous portion of the thyroid that is not removed (the other 'wing' of the butterfly-shaped thyroid) will continue to make thyroid hormone, often enough to avoid needing to take a thyroid hormone replacement pill after surgery. In contrast, a person who has a total thyroidectomy will not have any thyroid tissue left to make thyroid hormone after surgery and will have to take a thyroid hormone pill each day, for the rest of their life. Second, the risks related to undergoing thyroid surgery, in particular voice hoarseness and permanently low body levels of calcium, are lower for thyroid lobectomy than for total thyroidectomy.

A major disadvantage of thyroid lobectomy, compared to total thyroidectomy, however, is that the remaining thyroid not removed during surgery may also contain or, at some point may form, another papillary thyroid cancer, especially if nodules are already present in this remaining thyroid tissue. The authors of the research described here sought to study the risk of papillary thyroid cancer being present, or developing over time, for people who

underwent thyroid lobectomy for treatment of papillary thyroid cancer and for whom nodules were known to be present in that thyroid tissue not removed during surgery.

### FULL ARTICLE TITLE

Pak SJ et al Contralateral low-to-intermediate suspicion nodule is not a contraindication for lobectomy in patients with papillary thyroid carcinoma. *Thyroid*. Epub 2023 Aug 25. PMID: 37624735

### SUMMARY OF THE STUDY

The authors of this work reviewed the medical records for everyone who had a thyroid lobectomy for treatment of papillary thyroid cancer at their institution between January 2016 and December 2017. This included 1761 people, 700 of whom were known to have at least one nodule in that part of the thyroid not removed during surgery. Over time, 54% of these nodules stayed the same, became smaller or disappeared altogether. These findings are reassuring, as cancerous nodules tend to grow. On the other hand, 14.8% of nodules grew over time, which raises concern for the presence of thyroid cancer. Overall, 20 of the 700 people (2.9%) having nodules in the thyroid tissue not removed during thyroid lobectomy were ultimately found to have papillary thyroid cancer in this remaining thyroid tissue. However, the 5-year survival rate (which was excellent at 98.7%) was the same for people having known nodules in the thyroid tissue not removed during thyroid lobectomy compared to people without such nodules. The authors did find that having nodules in the thyroid tissue not removed during thyroid lobectomy was associated with higher risk of this cancer in the remaining thyroid tissue, especially if ultrasound of these nodules showed features suspicious for thyroid cancer. The authors also found that these nodules tended to grow over time, especially if they were bigger than 1 cm in diameter at the time of thyroid lobectomy.



## THYROID CANCER, continued

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This work shows that for people diagnosed with papillary thyroid cancer who are candidates for thyroid lobectomy, but who also have known nodules in the thyroid tissue that would be left behind after this surgery, thyroid lobectomy is a reasonable treatment choice. This is especially true if ultrasound of these nodules does not show any features suspicious for cancer. These findings are

encouraging, as thyroid lobectomy may allow a person to avoid the need to take a thyroid hormone replacement pill after surgery and has lower risks of complications during surgery compared to total thyroidectomy. This being said, this study also indicates that nodules in the thyroid not removed during thyroid lobectomy should be monitored over time, as a small number of these will be cancerous and will need to be treated with additional surgery.

— Jason D. Prescott, MD PhD

### ATA RESOURCES

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

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

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

### 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.

**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).

**Total thyroidectomy:** surgery to remove the entire thyroid gland.

**Lobectomy:** surgery to remove one lobe of the thyroid.



## HYPOTHYROIDISM

# Safety of levothyroxine plus liothyronine (T4/T3) therapy in postsurgical hypothyroidism

### BACKGROUND

The standard of care for treatment of hypothyroidism is levothyroxine to return the thyroid hormone levels to the normal range. However, some patients have continued symptoms while on levothyroxine alone. Thyroxine is converted in the body to T3 (liothyronine), the active thyroid hormone. In patients without a thyroid, such as after a total thyroidectomy, T3 levels may not be as high on levothyroxine alone as they were when the thyroid was intact. Because of this, some have tried a combination of levothyroxine and liothyronine (T4/T3 therapy) to try to treat continued symptoms on levothyroxine alone in patients with postsurgical hypothyroidism. Indeed, some patients experience improvement on this combination therapy. One concern about including liothyronine in the treatment of hypothyroidism is the possibility that T3 levels may be raised too high and affect the heart and cause problems. In this study, investigators evaluated the effects of T4/T3 therapy on heart function parameters in healthy patients that have undergone thyroidectomy for thyroid cancer.

### THE FULL ARTICLE TITLE

Biondi B et al. Preliminary results of a double-blind randomized controlled trial evaluating the cardiometabolic effects of levothyroxine and liothyronine compared to levothyroxine with placebo in athyreotic low-risk thyroid cancer patients. *Thyroid*. 2023;33(12):1402-1413; doi: 10.1089/thy.2023.0135. PMID: 37725587.

### SUMMARY OF THE STUDY

A total of 300 patients with postsurgical hypothyroidism on long-term levothyroxine therapy who had history of total thyroidectomy and radioiodine ablation for low-risk thyroid cancer were considered for this trial. Of these patients, 28 met inclusion criteria and were randomly assigned to either receive: (a) T4/T3 treatment or (b) T4/placebo treatment. There were 14 patients in each group. A total of 50 healthy volunteers with normal thyroid function were matched for sex, age, physical activity, and lifestyle and participated as controls.

Assessments included blood pressure, heart rate, height, weight, body-mass index and waist and hip circumferences), TSH, free triiodothyronine (FT3), free thyroxine (FT4), electrocardiography (ECG), color Doppler echocardiography (echo), and questionnaires to assess symptoms and signs of hyperthyroidism (symptom rating scale). The thyroid function tests and questionnaires were performed at baseline and after 3, 6, and 12 months. ECG, echo, and the other data were assessed at baseline and after 6 and 12 months. All data were compared with the results obtained from the 50 healthy volunteers. The T3 was administered orally in liquid drops at an initial ratio of 17:1 (T4:T3) and the daily T3 or placebo dosage was divided into two doses, one in the morning and the other 12 hours later. There were no deaths and no arrhythmias, angina, heart failure, stroke, or other serious adverse events; no potential risks were detected in patients in either group. The average levothyroxine dose in the whole group of patients was 1.97 µg/kg/day (range, 1.68–2.16) to achieve a serum TSH goal between 0.3 and 2 mIU/L.

After 12 months of treatment, serum TSH, serum FT4, body weight, BMI, waist circumference, and hip circumference did not significantly differ in the T4/T3 group as compared with the T4/placebo group. However, FT3 was significantly higher in the T4/T3 group than in the T4/placebo group. The hyperthyroid symptom score was not significantly different. Regarding the color Doppler echo data, one of the diastolic cardiac markers did not differ between the volunteers and the T4/T3 group after 12 months of treatment while it was worse in the T4/placebo group.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that the combination T4/T3 therapy was safe in this small group of thyroid cancer patients with post-surgical hypothyroidism. Further, the patients in the T4/T3 group had the same hyperthyroid score as those in



## HYPOTHYROIDISM, continued

the T4/placebo group. Interestingly, the only parameter that differed between the 2 groups was an measure of heart function, where those in the T4/placebo group had a worse score than the T4/T3 group and the normal volunteers. This study suggests T4/T3 may be a treatment

option in patients with postsurgical hypothyroidism. More studies are needed to determine the role and safety of combination T4/T3 treatment on patients with other causes of hypothyroidism.

— Alan P. Farwell, MD

### ATA RESOURCES

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

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

**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.

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

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

**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.



# Clinical Thyroidology® for the Public

## 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.



ThyCa: Thyroid Cancer Survivors' Association, Inc.  
[www.thyca.org](http://www.thyca.org)



MCT8 - AHDS Foundation

THYROID CANCER ALLIANCE



### American Thyroid Association®

[www.thyroid.org](http://www.thyroid.org)

ATA® Patient Resources:

[www.thyroid.org/thyroid-information/](http://www.thyroid.org/thyroid-information/)

Find a Thyroid Specialist: [www.thyroid.org](http://www.thyroid.org)

(Toll-free): 1-800-THYROID

[thyroid@thyroid.org](mailto:thyroid@thyroid.org)

### Bite Me Cancer

[www.bitemecancer.org](http://www.bitemecancer.org)

[info@bitemecancer.org](mailto:info@bitemecancer.org)

### Graves' Disease and Thyroid Foundation

[www.gdatf.org](http://www.gdatf.org)

(Toll-free): 877-643-3123

[info@ngdf.org](mailto:info@ngdf.org)

### Light of Life Foundation

[www.checkyourneck.com](http://www.checkyourneck.com)

[info@checkyourneck.com](mailto:info@checkyourneck.com)

### MCT8 – AHDS Foundation

[mct8.info](http://mct8.info)

Contact@[mct8.info](mailto:mct8.info)

### Thyca: Thyroid Cancer Survivors' Association, Inc.

[www.thyca.org](http://www.thyca.org)

(Toll-free): 877-588-7904

[thyca@thyca.org](mailto:thyca@thyca.org)

### Thyroid Cancer Alliance

[www.thyroidcanceralliance.org](http://www.thyroidcanceralliance.org)

[www.thyroidcancerpatientinfo.org](http://www.thyroidcancerpatientinfo.org)

Rotterdam, The Netherlands

### Thyroid Federation International

[www.thyroid-fed.org](http://www.thyroid-fed.org)

[tfi@thyroid-fed.org](mailto:tfi@thyroid-fed.org)

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