Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

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 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.

December is Thyroid and Development Awareness Month.

In this issue, the studies ask the following questions:

- Is the dose of levothyroxine in thyroid cancer patients related to the risk of developing secondary primary cancers?
- Can the behavior of thyroid cancer be predicted by the initial biopsy results?
- Is thyroid lobectomy a safe and effective treatment for thyroid cancer?
- Do proton pump inhibitor drugs used for reflux affect absorption of liquid levothyroxine?
- Can cancer drugs for non-thyroid cancer cause thyroid problems?
- Do patients with Graves' disease have to be screened for other autoimmune diseases?

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

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

THYROID CANCER

Levothyroxine dosage and the increased risk of second cancer in thyroid cancer survivors

BACKGROUND

Thyroid cancer is common and has an excellent prognosis. Treatment of thyroid cancer includes thyroid surgery in most cases. In patients with more advanced thyroid cancer, surgery can be followed by radioactive iodine (RAI) treatment and long-term thyroid hormone therapy with levothyroxine to decrease the risk of cancer recurrence. Because of these effective treatments, most patients live long lives after the diagnosis of thyroid cancer even if the cancer is not completely cured.

Some studies suggest that thyroid cancer patients have a higher risk of developing second primary cancers (SPCs) compared to the general population. It is known that RAI treatment, especially at higher doses, increases the risk of SPCs, especially blood cancers. Also, based on the risk of thyroid cancer recurrence, the thyroid hormone therapy may be adjusted to keep TSH levels in the normal range, slightly low or completely suppressed. The impact of the range of thyroid hormone treatment on SPCs has not been investigated. There is evidence that thyroid hormones are involved in the regulation of cellular growth and multiplication. The goal of this study is to evaluate the relationship between the levothyroxine dose and the risk of developing SPCs in thyroid cancer survivors.

THE FULL ARTICLE TITLE

Kim MS, et al. Risk of subsequent primary cancers in thyroid cancer survivors according to the dose of levothyroxine: a nationwide cohort study. Endocrinol Metab (Seoul) 2024;39:288-299; doi: 10.3803/EnM.2023.1815. PMID: 38437824.

SUMMARY OF THE STUDY

This nation-wide population-based study included 342,920 thyroid cancer patients (average age of 48 years; 81% female) who underwent thyroidectomy between 2004 and 2018 in Korea. The study data was retrieved from the Korean National Health Insurance Service (NHIS) database, which stores the medical information of the entire Korean population. Patients diagnosed with cancers within 2 years from the date of thyroid cancer diagnosis and those taking levothyroxine (LT4) before the thyroid cancer diagnosis were excluded.

The study patients were divided in two groups: non-LT4 and LT4, based on whether they started to take LT4 after the thyroid surgery, with the LT4 group being further divided in four subgroups based on the LT4 dose. The study evaluated the development of SPCs in the non-LT4 versus LT4 groups, and also in different LT4 dose subgroups after the thyroid cancer treatment. The analysis was adjusted for multiple factors, including the total dose of RAI treatment, type of thyroid surgery, patient adherence to LT4, obesity, smoking and alcohol consumption.

Over an average follow-up of 7 years, 849 (6.3 per 1000 person-year) SPCs were diagnosed in the non-LT4 group and 16,561 (6.9 per 1000 person-year) SPCs were diagnosed in the LT4 group. The risk of colorectal, liver, and biliary tract cancer was higher in the LT4 group compared to the non-LT4 group, after adjustment for age, gender and total dose of RAI treatment. In the LT4 group, the risk of all SPCs increased with increasing LT4 dose. There was a gradual increase in the risk of digestive system cancers with the increase in the LT4 dose, with a significant risk noted in the high-dose LT4 groups. In addition to the digestive system cancers, the risks of most cancers, including head and neck, lung, breast, female genital system, brain, and hematologic cancers increased in the high-dose LT4 groups as compared to the lowest LT4 dose group.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study showed for the first time that high dose LT4 treatment was associated with an increased risk of second primary cancers in thyroid cancer patients, independent

THYROID CANCER, continued

of the RAI treatment. While thyroid hormone suppression therapy is important in prevention of thyroid cancer recurrence, its long-term use, particularly at high doses, may increase the risk of developing these SPCs, especially digestive cancers. Additional research is needed to find the best LT4 dosage to balance benefits and possible risks of thyroid hormone treatment in thyroid cancer patients.

— Alina Gavrila, MD, MMSC

ATA RESOURCES

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

Radioactive Iodine Therapy: https://www.thyroid.org/radioactive-iodine/

ABBREVIATIONS & DEFINITIONS

Thyroid cancer: includes papillary thyroid cancer (PTC), the most common type of thyroid cancer and follicular thyroid cancer (FTC), the second most common type of thyroid cancer.

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* (usually one lobe with or without the isthmus).

Levothyroxine (T4): 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.

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*).

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

THYROID NODULES

Can the behavior of thyroid cancer be predicted by the initial biopsy results?

BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of the population. The concern about any thyroid nodule is whether it is a cancer. Overall, only 5-6% of thyroid nodules are cancer. The best way to determine of a nodule is cancer is to perform a thyroid biopsy. When a patient has a thyroid biopsy, there are 6 potential categories for the result based on their increasing risk of being cancer. These categories are the Bethesda scoring system. Bethesda I is non-diagnostic, meaning there are not enough cells to make a diagnosis, and Bethesda II is a benign result. Bethesda III and IV are atypical results in that the cells are not normal or abnormal. Bethesda V is suspicious for thyroid cancer and Bethesda VI is most likely to be thyroid cancer.

Overall, 20% thyroid nodule biopsies will fall into the Bethesda III or IV category, giving a risk of cancer ranging from 15-35%. The risk of cancer for Bethesda V biopsies is 65-74% and the risk of cancer in Bethesda VI biopsies is 94-97%. There are no long-term studies on how cancers in each of these Bethesda categories behave. The aim of the study is to separate cancers into categories based on their initial Bethesda category and monitor how each of the cancer in each category behaves.

THE FULL ARTICLE TITLE

Endo M et al. Indolent behavior of malignant Bethesda III nodules compared to Bethesda V/VI nodules. J Clin Endocrinol Metab 2024;109(9):2317-2324; doi: 10.1210/clinem/dgae108. PMID: 38415340.

SUMMARY OF THE STUDY

At a single hospital, all thyroid nodules biopsied and categorized as Bethesda III, IV, V, and VI in adults that were later found to be cancer were analyzed from 2007 to 2018. Small (<0.5 cm) thyroid cancers initially biopsied as Bethesda III or IV and medullary thyroid cancers were not considered in the study. Out of 556 cases, 69% of the patients were women, the average age was 48.4 years, and the Bethesda categories were spread out as follows: 87 Bethesda III, 109 Bethesda IV, 120 Bethesda V, and 240 Bethesda VI.

Bethesda categories III, IV, and VI were more likely to contain papillary thyroid cancer than Bethesda category V. Having more than one area of cancer in the sample and having a *BRAF V600e* genetic mutation was also more likely in Bethesda categories III, V, and VI as compared to Bethesda category IV. A mutation called *NRAS* seemed more likely to be found in Bethesda IV than Bethesda III biopsied nodules, but it was not an obvious enough difference to be significant.

Compared to the Bethesda III category, the Bethesda V and VI biopsied nodules were more likely to undergo a total thyroidectomy, have a more advanced cancer, including spread to the lymph nodes, invasion beyond the thyroid capsule, and an increased rate of recurrence after the initial treatment. The Bethesda V and VI nodules were less likely to ever be in a state where there was no evidence of disease compared to Bethesda III. Although Bethesda IV nodules were more likely to have spread into the lymphatic and blood vessels than Bethesda III nodules, otherwise there was no difference in cancer staging, extension beyond the thyroid capsule, likelihood of receiving radioactive iodine treatment, recurrence rate after initial treatment, spread to lungs or bones, or likelihood of dieing.

When comparing Bethesda categories III and IV to Bethesda categories V and VI, the latter group was more likely to have lymph node spread, multiple areas of cancer within the surgical sample, extension beyond the thyroid capsule, likelihood of having the *BRAF V600e* gene mutation, and spread to the lungs and bones. The Bethesda V and VI categories were less likely to ever be in a state where there was no evidence of disease compared to Bethesda III and IV categories.

THYROID NODULES, continued

Only 7 out of the 87 Bethesda III category nodules eventually contained cancer that spread into the neck, lung, or bones after initial treatment, and all seven patients had thyroid nodules measuring larger than 2.5 cm. Overall, 2 of these 7 patients already had spread to the lungs and bones when the nodule was biopsied as Bethesda III category.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that thyroid cancers with initial Bethesda III biopsies are less likely to be aggressive cancers having extension beyond the thyroid capsule, spread to the lymph nodes, and more likely to achieve a state with no evidence of disease compared to Bethesda V and VI nodules. As such, if a patient has a nodule that has a Bethesda III biopsy, particularly it measures less than 2.5 cm, active surveillance (watching the nodule with ultrasound without surgery) or less aggressive initial treatment could be considered. This is an important finding and helps physicians and patients to determine the best treatment option for an individual patient.

— Pinar Smith, 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 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 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.

Inadequate/Insufficient biopsy: this happens with not enough cells are obtained during the biopsy to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

Non-diagnostic thyroid biopsy: this happens when some atypical cells are found but not enough to provide a diagnosis. This occurs in 5-10% of biopsies. This often results in the need to repeat the biopsy.

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.

Atypical thyroid biopsy: this happens when there are some abnormal/atypical cells in the biopsy sample but not enough to diagnose a cancer. However, because there are abnormal cells in the biopsy sample, the specimen cannot be called benign. Sometimes a repeat biopsy may be helpful but often surgery is recommended to remove the nodule.

THYROID NODULES, continued

Suspicious thyroid biopsy: this happens when there are atypical cytological features suggestive of, but not diagnostic for malignancy. Surgical removal of the nodule is required for a definitive diagnosis.

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).

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

BRAF gene: this is gene that codes for a protein that is involved in a signaling pathway and is important for cell growth. Mutations in the BRAF gene in adults appear to cause cancer.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

THYROID CANCER

Surgery to remove only part of the thyroid for treatment of thyroid cancer is becoming more common: is this a safe option?

BACKGROUND

Treatment of cancer in the thyroid gland, a butterfly-shaped organ in the front part of the neck that makes thyroid hormone, generally requires thyroid surgery. In the past, the most common way to treat thyroid cancer was removal of the whole thyroid gland (called a total thyroidectomy). A major reason for this was that doctors were afraid that if any thyroid tissue was left behind after initial thyroid cancer surgery, this cancer might come back in the remaining thyroid tissue (called cancer recurrence). If this were to happen, more surgery might be needed to remove the recurrent cancer. Such repeat surgery is often more difficult than the first surgery, with higher risk of surgical complications. In addition, total thyroidectomy has significant drawbacks/risks compared to removal of just that part of the thyroid that contains cancer (called a thyroid lobectomy). These include lifelong need to take a daily thyroid hormone pill after surgery as well as the low risk of surgical complications, including risk of permanent low body calcium levels after surgery, voice changes after surgery and risk of breathing problems requiring placement of a tracheostomy tube (a breathing tube that goes through the skin into the windpipe to breathe through).

Recent studies have suggested that thyroid lobectomy for treatment of thyroid cancer is safe and that the risk of cancer recurrence in that thyroid tissue not removed during surgery is very low. For this reason, and also because of the lower risks and fewer drawbacks associated with partial thyroid removal, thyroid lobectomy for treatment of thyroid cancer is becoming increasingly common. Indeed, the American Thyroid Association (ATA) guidelines for the treatment of thyroid cancer published in 2015 recommend thyroid lobectomy as an option for people undergoing surgery for thyroid cancer.

The authors of the study described here further address whether thyroid lobectomy is an acceptable treatment for thyroid cancer by comparing the risk of thyroid cancer recurrence between people undergoing total thyroidectomy and people having a thyroid lobectomy.

FULL ARTICLE TITLE

Kheng M, et al. Reoperation rates after initial thyroid lobectomy for patients with thyroid cancer: a national cohort study. Thyroid. Epub Jul 25 2024; doi: 10.1089/thy.2024.0128. PMID: 39049736.

SUMMARY OF THE STUDY

The authors of this study reviewed medical insurance claims records for adults who underwent either total thyroidectomy or thyroid lobectomy for the treatment of thyroid cancer at over 1000 different United States Hospitals. The frequency of total thyroidectomy compared to thyroid lobectomy was evaluated for thyroid cancer patients who underwent thyroid surgery before 2015 to those whose thyroid surgery occurred after publication of the 2015 ATA guidelines. Thyroid cancer recurrence over time was evaluated for each group.

A total of 65,627 thyroid cancer patients were included in the study, with the rate of thyroid lobectomy for treatment increasing from 21% in the 2 years prior to 2015, to 37% in the subsequent 5 years. This increased thyroid lobectomy rate was slightly higher when the operation was performed at an institution specializing in this kind of surgery (called a high-volume center). Overall, the rate of cancer recurrence was found to be similar between thyroid cancer patients undergoing total thyroidectomy and those for whom thyroid lobectomy was performed.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This work adds to the growing body of evidence supporting thyroid lobectomy as a management alternative for thyroid cancer and indicates that selection of this option is increasingly frequent. The study authors found that the risk of thyroid cancer recurrence following thyroid lobectomy is similar to that seen when total thy-

THYROID CANCER, continued

roidectomy is performed for thyroid cancer. Moreover, the surgical complication risk associated with thyroid lobectomy is lower than that of total thyroidectomy and, unlike total thyroidectomy, many people do not need to take a thyroid hormone pill after thyroid lobectomy. Finally, this work indicates that thyroid cancer surgeons do take new published treatment guidelines into account when considering treatment options for people diagnosed with thyroid cancer. Although the ultimate choice regarding the extent of thyroid surgery should always involve an individualized discussion between a person diagnosed with thyroid cancer and their surgeon, the results of this study, taken together, support thyroid lobectomy as a safe treatment option.

— Jason D. Prescott, MD PhD

ATA RESOURCES

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

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

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).

Total thyroidectomy: surgery to remove the entire thyroid gland.

Lobectomy: surgery to remove one lobe of the thyroid.

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

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

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

HYPOTHYROIDISM

Use of proton pump inhibitors and levothyroxine

BACKGROUND

Levothyroxine is the most commonly used medication to treat hypothyroidism. Levothyroxine is usually taken in pill form. After swallowing the levothyroxine, the pill then dissolved in the stomach by the stomach acids and then absorbed intothe bloodstream in the small intestine. We know that some gastrointestinal conditions can affect the levothyroxine absorption; for example, celiac disease and inflammatory bowel disease. Certain medications can decrease the absorption of levothyroxine in the instestines. One such class of medications are proton-pump inhibitors (PPIs) which lower the amount of acid the stomach makes and are an effective treatment for reflux disease. Because of the decrease in the stomach acid, the levothyroxine pill may not be dissolved completely and the absorption of the levothyroxine may be decreased. Thus, patients may need frequent adjustments of their levothyroxoine treatment dose.

One brand of levothyroxine, Tirosint, is liquid that can be taken in a gelcap or as a liquid (Tirosint-SOL). Since the liquid form does not need to be dissolved, then the effect of PPIs on levothyroxine absorption should be minimal. In this study, the authors wanted to find out if PPIs affect the absorption of liquid levothyroxine (Tirosint- SOL).

THE FULL ARTICLE TITLE

Seng Yue C et al. Proton pump inhibitors do not affect the bioavailability of a novel liquid formulation of levothyroxine. Endocr Pract 2024;30(6):513-520; doi: 10.1016/j.eprac.2024.03.388. PMID: 38554774.

SUMMARY OF THE STUDY

The authors studied 36 healthy men and women. They were divided in three groups: *Group 1*: took a single dose of 600 mcg of liquid levothyroxine together with 40 mg of omeprazole (a PPI). *Group 2*: took liquid levothyroxine in the morning and omeprazole in the evening. *Group 3*: took liquid levothyroxine alone. Blood samples to measure a thyroid hormone (total thyroxine, TT4) were taken before, and then at different time intervals up to 48 hours after taking the liquid levothyroxine dose.

The average age of the participants was 40 years old. The baseline TSH was 1.75 mIU/L. Most of the participants were male and white. The levels of TT4 were similar in the three groups: there was no difference in the TT4 levels in the participants taking liquid levothyroxine together with PPIs or after spacing their intake by several hours, as compared to the levels of the participants taking liquid levothyroxine only.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Even though previous studies suggest that PPIs affect levothyroxine absorption, this small study shows that the absorption of liquid levothyroxine is not affected by PPIs. This study suggests that liquid levothyroxine may be a better treatment option for patients with hypothyroidism that are also taking medications such as PPIs. This may be especially important for patients who are not taking PPIs on a regular basis, but on and off, as it is often the case, and in this way, avoid swings of the thyroid levels.

— Susana Ebner MD

ATA RESOURCES

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

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

HYPOTHYROIDISM, continued

ABBREVIATIONS & DEFINITIONS

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

Levothyroxine (T4): 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.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

THYROIDITIS

Combination cancer immunotherapy drugs for non-thyroid cancer increase the risk of thyroiditis.

BACKGROUND

New drugs that use the body's immune system to attack cancer, called immunotherapy, have been a major breakthrough in treating non-thyroid cancer. Indeed, drugs called anti-programmed cell death ligand-1 antibody (PD-(L)1-Ab) do have a side effect of occasionally attacking the thyroid, causing autoimmune thyroiditis and hypothyroidism. Another class of cancer drugs, known as Tyrosine kinase inhibitors (TKIs) also have been shown to cause hypothyroidism. Both of these drugs can treat cancer alone or in combination.

This study examined the frequency, and clinical characteristics of thyroid problems caused by combination therapy with PD-(L)1-Ab and TKI cancer immunotherapy drugs.

THE FULL ARTICLE TITLE

Kobayashi T et al. Combined use of tyrosine kinase inhibitors with PD-(L)1 blockade increased the risk of thyroid dysfunction in PD-(L)1 blockade: a prospective study. Cancer Immunol Immunother 2024;73(8):146; doi: 10.1007/s00262-024-03733-2. PMID: 38833157.

SUMMARY OF THE STUDY

This study included patients treated with a PD-(L)1-Ab drug alone or in combination with TKI drugs between November 2, 2015, and July 12, 2023, at Nagoya University Hospital. Thyroid function tests and thyroid autoantibodies (TPO and thyroglobulin antibodies) were measured in all patients and TSH receptor antibody measured in patients who developed hyperthyroidism at baseline prior to starting the drugs and during follow-up.

The study included 757 patients: 734 (97%) were treated with PD-(L)1-Ab alone and 23 (3%) were treated with PD-(L)1-Ab and TKI together. The total number of patients with autoimmune thyroiditis were significantly higher in patients treated with PD-(L)1-Ab in combination with TKI than in those treated with PD-(L)1-Ab alone for autoimmune thyroiditis (4 of 23, 17.4% vs. 45 of 734, 6.1%), isolated hypothyroidism (10 of 23, 43.5% vs. 29 of 734, 4.0%) and all thyroid problems (14 of 23, 60.9% vs. 74 of 734, 10.1%). All patients with positive TPO or thyoglobulin antibodies at baseline developed thyroid problems after PD-(L)1-Ab in combination with TKI treatment, which was a significantly higher risk than in patients negative for these thyroid antibodies at baseline (4 of 4, 100% vs. 10 of 19, 52.6%). The average time to the development of thyroid problems did not differ significantly between the PD-(L)1-Ab alone group (48 days) and the PD-(L)1-Ab in combination with TKI group (58 days).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study confirms that the use of cancer immunotherapy drugs for non-thyroid cancer frequently cause thyroid problems, including thyroiditis and hypothyroidism. This study also shows that the risk of developing thyroid problems is more common when using these drugs in combination as compared to using these drugs alone. Further, patients with positive thyroid antibodies are at a much higher risk of developing thyroid problems on these drugs. This is important in monitoring patients on these cancer drugs for the development of thyroid problems.

— Alan P. Farwell, MD

ATA RESOURCES

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

Thyroiditis: https://www.thyroid.org/thyroiditis/

THYROIDITIS, continued

ABBREVIATIONS & DEFINITIONS

Immune system: a system of organs, tissues, and cells in our body that has the role to recognize potentially harmful foreign substances and organisms as well as abnormal body cells and produce antibodies to destroy these factors.

Antibodies: proteins that are produced by the body's immune cells that attack and destroy bacteria and viruses that cause infections. Occasionally the antibodies get confused and attack the body's own tissues, causing autoimmune disease.

Thyroiditis: inflammation of the thyroid, most commonly cause by antibodies that attack the thyroid as seen in Hashimoto's thyroiditis and post-partum thyroiditis. It can also result from an infection in the thyroid.

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

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

Clinical Thyroidology® for the Public

GRAVES' DISEASE

One in six patients with Graves' disease will develop another autoimmune disease— why knowing about polyautoimmunity is important

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism in the United States. It is an autoimmune disease, meaning that it is caused by the immune system that gets confused and attacks the bodies cells rather than those causing infection. In Graves' disease, the immune system produces antibodies (thyroid stimulating antibodies) that bind to the TSH receptor on the surface of thyroid cells. When these antibodies bind to thyroid cells, they are turned on and the gland becomes enlarged and overactive (called hyperthyroidism), leading to an high levels of thyroid hormones in the blood. Graves' disease can also cause swelling behind the eyes, a phenomenon known as thyroid eye disease (TED), which can make the eyes bulge and, in severe cases, affect vision.

Autoimmune diseases often "cluster" in patients, meaning that having one autoimmune disease increases the likelihood of developing another. Thus, patients with Graves' disease are more likely to develop another autoimmune disease unrelated to the thyroid (called non-thyroid autoimmune disease). In general, most patients with Graves' disease just have Graves' disease. Until now, most research has looked at the presence of autoimmune thyroid disease in people who had other autoimmune conditions, such as systemic lupus erythematosis. However, this study looked at the opposite: it examined the risk of developing other autoimmune diseases in people who already have Graves' disease.

THE FULL ARTICLE TITLE

Sohn SY, et al. Risk of non-thyroidal autoimmune diseases in patients with Graves' disease: a nationwide retrospective cohort study. Rheumatology (Oxford). Epub 2024 Jan 5.

SUMMARY OF THE STUDY

The authors studied 77,401 patients in Korea who were newly diagnosed with Graves' disease between 2008 and 2012. The average age was 48.8 years and 65% were women. These patients were compared to an equal number of age- and sex-matched controls. The study looked at how often non-thyroid autoimmune diseases were diagnosed. These diseases included lupus, Sjogren's syndrome, vitiligo, alopecia areata, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, and Behçet's disease. The goal was to determine if people with Graves' disease had a higher risk of developing these conditions compared to those without Graves' disease.

Over an average follow-up of 9 years, 16.1% of patients with Graves' disease (12,341 people) developed a non-thyroid autoimmune disease. On average, these conditions were diagnosed at 50.8 years of age, about 5.3 years after the initial diagnosis of Graves' disease. Compared to the group without Graves' disease, patients with Graves' disease had a 15% higher risk of developing lupus, a 24% higher risk of vitiligo, and an 11% higher risk of alopecia areata. Additionally, patients with Graves' disease who also had developed thyroid eye disease faced an even greater risk of certain autoimmune conditions. Those with eye disease were significantly more likely to develop lupus, ankylosing spondylitis, and Sjogren's syndrome compared to Graves' patients without eye findings.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this large national study, 16.1% of patients who were newly diagnosed with Graves' disease developed another autoimmune disease within an average of 5 years. Doctors need to be aware of this connection so they can carefully monitor their patients with Graves' disease for signs of other autoimmune disorders.

— Philip Segal, MD

GRAVES' DISEASE, continued

ATA RESOURCES

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.

Thyroid eye disease (TED): also known as Graves ophthalmopathy. TED is most often seen in patients with Graves' disease but also can be seen with Hashimoto's thyroiditis. TED includes inflammation of the eyes, eye muscles and the surrounding tissues. Symptoms include dry eyes, red eyes, bulging of the eyes and double vision.

Autoimmune disorders: A diverse group of disorders that are caused by antibodies that get confused and attack the body's own tissues. The disorder depends on what tissue the antibodies attack. Graves' disease and Hashimoto's thyroiditis are examples of autoimmune thyroid disease. Other Autoimmune disorders include: type 1 diabetes mellitus, Addison's disease (adrenal insufficiency), vitiligo (loss of pigment of some areas of the skin), systemic lupus erythematosus, pernicious anemia (B12 deficiency), celiac disease, inflammatory bowel disease, myasthenia gravis, multiple sclerosis, and rheumatoid arthritis.

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).

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

Volume 17 | Issue 12 | December 2024

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.

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

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

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 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